PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07H 19/01, C07D 405/14 C07D 407/06, 407/14, 409/14 C07D 413/14, 417/14 A61K 31/70	A1	**(11) International Publication Number:** WO 93/06118
		(43) International Publication Date: 1 April 1993 (01.04.93)

(21) International Application Number: PCT/GB92/01760

(22) International Filing Date: 24 September 1992 (24.09.92)

(30) Priority data:

9120491.7	26 September 1991 (26.09.91)	GB
9201507.2	24 January 1992 (24.01.92)	GB
9219053.7	9 September 1992 (09.09.92)	GB

(71) Applicant *(for all designated States except US):* SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

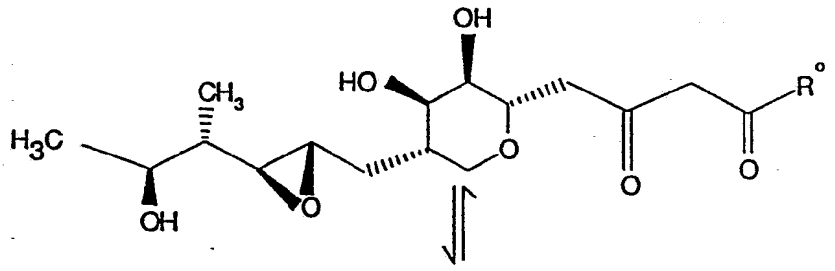
(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* BROOM, Nigel, John, Perryman [GB/GB]; O'HANLON, Peter, John [GB/GB]; ELDER, John, Stephen [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB).

(74) Agent: TYRRELL, Arthur, William, Russell; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
With international search report.

(54) Title: ANTIBACTERIAL, ANTIMYCOPLASMAL COMPOUNDS RELATED TO MUPIROCIN



(I)

(57) Abstract

This invention relates to a novel class of mupirocin derived compounds of Formula (I) having a modification of the C-1 to C-3 fragment. The β-diketone compounds of Formula (I) are useful as antibacterial and antimycoplasmal agents. The compounds of this invention are represented by formula (I) wherein R^0 is a hydrocarbyl or heterocyclic group.

FOR THE PURPOSES OF INFORMATION ONLY

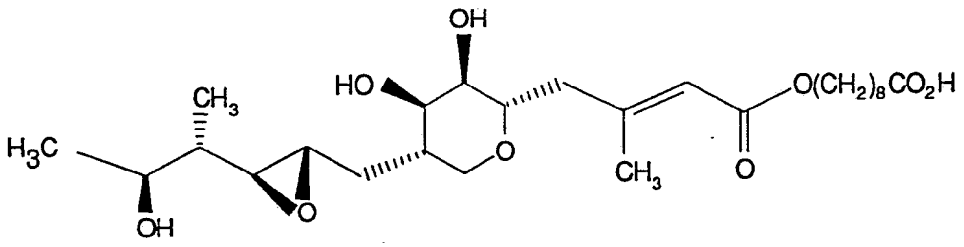
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SK	Slovak Republic
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
UA	Ukraine
US	United States of America

ANTIBACTERIAL,ANTIMYCOPLASMAL COMPOUNDS RELATED TO MUPIROCIN

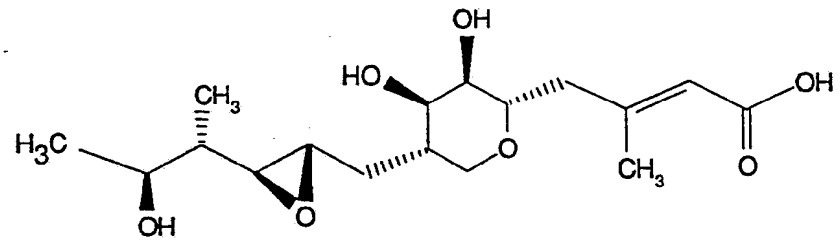
This invention relates to a novel class of compounds having antibacterial and antimycoplasmal activity, to processes for their preparation and to their use in human and veterinary medicine, and also to intermediates for use in the preparation of such compounds.

Mupirocin, the compound of formula (A):



(A)

exhibits good activity against Gram positive bacteria, H.influenzae, Legionella and mycoplasma. It is marketed as a topical formulation by Beecham Group p.l.c. under the trade mark BACTROBAN. Mupirocin (formerly known as pseudomonic acid) is rapidly hydrolysed in vivo to monic acid A, the compound of formula (B):



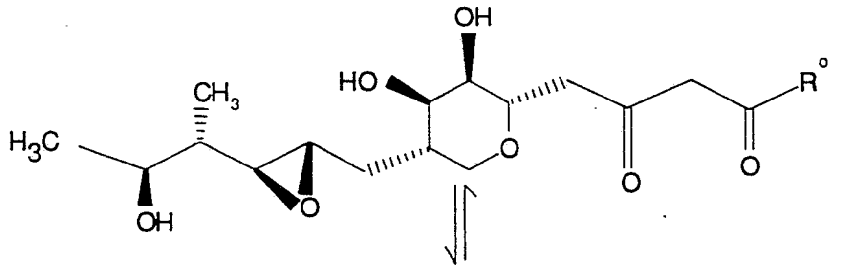
(B)

which is inactive.

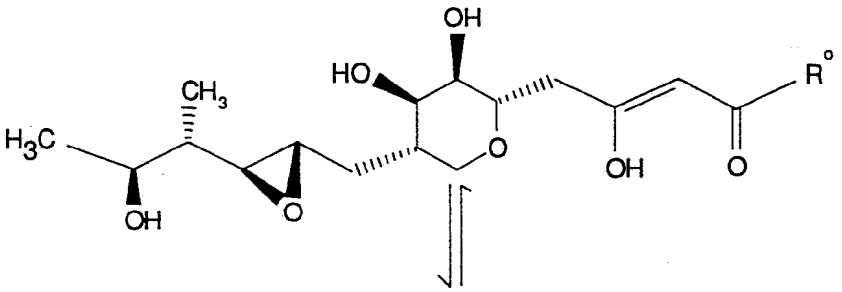
Various proposals have been made to improve the metabolic stability of mupirocin with respect to enzymatic hydrolysis by varying the nature of the C-1 to C-3 fragment, for instance, by modification of the C-1 ester functional group. Examples of this strategy include C-1 heterocyclic derivatives (EP-A-0 087 953 and EP-A-0 123 578, Beecham Group p.l.c.), C-1 amides (US 4 312 764, Beecham Group Ltd), and C-1 ketones, including inter alia aryl and heterocyclic ketones (US 4 312 874, Beecham Group Ltd, Klein et al, poster presented at the Third Annual Chemical Congress of North America, Toronto, June 1988, and J. Med. Chem. 1989, 32, 151). In addition, various modifications elsewhere in the C-1 to C-3 fragment, other than at C-1, have also been made, including β-ketoesters (Klein et al, ibid.), C-2 alkyl and C-2 halo derivatives (Crimmin M. J. et al; J. Chem. Soc., Perkin Trans.1, 1985, 549), and reduction of the C-2 C-3 double bond (Chain E.B. et al, J. Chem. Soc., Perkin Trans.1, 1977, 294). No improvement in the overall biological profile, compared with mupirocin, was, however, observed. Indeed, the β-ketoester is reported to have shown little if any antibacterial activity.

It has now been surprisingly found that alternative modification of the C-1 to C-3 fragment leads to compounds with an enhanced biological profile.

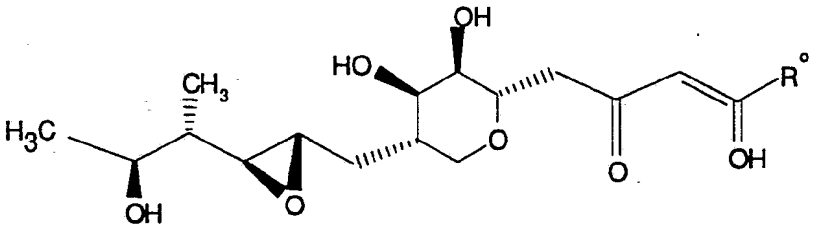
Accordingly, the present invention provides a compound of formula (IA), (IB) or (IC):



(IA)



(IB)



(IC)

wherein R^0 denotes a substituted or unsubstituted hydrocarbyl or heterocyclyl group. More specifically R^0 denotes the term $(A)_n$ - $(B)_m$; wherein n and m are integers having a value of 0 or 1; A is a (C_{1-6}) alkyl, (C_{2-6}) alkenyl, or (C_{2-6}) alkynyl group; B is a (C_{3-7}) cycloalkyl, (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group. Both A and B may be optionally substituted as herein below defined. In the R^0 moiety when n is 0 then A represents a bond, and when m is 0 then B represents hydrogen; m and n may not both represent 0 at the same time.

Suitably when n is 0 and m is 1, B is a substituted or unsubstituted (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group. B is preferably an aryl or heteroaryl moiety. More specifically, B is a cyclohexenyl, phenyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl, or thiazolyl group.

Suitably, when n is 1, m is 0, and B is hydrogen, then A is a (C_{1-6})alkyl moiety. A is preferably a substituted or unsubstituted butyl group.

Suitably, when n is 1, and m is 1, then A is a (C_{2-6})alkenyl, (C_{2-6})alkynyl group. Preferably, when n is 1, and m is 1, then B is a substituted or unsubstituted aryl or heteroaryl group, such as a furanyl or phenyl. More preferably A is an ethenyl or acetylenyl (ethynyl) group.

Suitably B is a substituted or un-substituted aryl or heteroaryl group. As used herein the term "(un)substituted" refers to both the substituted and unsubstituted derviative. Preferably B is a (un)substituted phenyl, (un)substituted pyrimidinyl, (un)substituted thiazolyl, (un)substituted oxazolyl, or (un)substituted pyridyl. More preferably B is an (un)substituted phenyl, (un)substituted pyridyl, or (un)substituted pyrimidinyl.

As defined herein both A or B may be optionally substituted, independently, with up to five, preferably up to three substituent groups, hereinafter referred to as X and X_1 respectively.

Examples of suitable X groups for A, when n is 1, include, cyano, amino, (C_{1-6})alkanoylamino, mono- or di- (C_{1-6})alkylamino, hydroxy, (C_{1-6})alkoxy, substituted (C_{1-6})alkoxy [also referred to as -O-R_1], (C_{1-6})alkylthio, (un)substituted heterocyclylthio, arylthio, (un)substituted sulphamoyl, (un)substituted carbamoyl, amidino, guanidino, nitro, halogen, carboxy and salts and esters thereof, (C_{1-6})alkanoyloxy, arylcarbonyloxy, heterocyclylcarbonyloxy, and acyl groups.

Suitably optional substituents (X_1), for B when m is 1, include, for example, (C_{1-6})alkyl, (poly)halo(C_{1-6})alkyl, cyano, (un)substituted heterocyclyl, amino, (C_{1-6})alkanoylamino, mono- or di-(C_{1-6})alkylamino, substituted mono- or di-(C_{1-6})alkylamino, [also referred to as -NR_2R_3], hydroxy, (C_{1-6})alkoxy, substituted (C_{1-6})alkoxy [also referred to as -O-R_1], (C_{1-6})alkenoxy, hydroxy substituted (C_{1-6})alkoxy, (un)substituted heterocyclylthio, arylthio, arylsulphinyl, arylsulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, (un)substituted sulphamoyl, (un)substituted carbamoyl, amidino, guanidino, nitro, halogen, carboxy

and salts and esters thereof, (C_{1-6}) alkylcarbonyloxy, arylcarbonyloxy, heterocyclylcarbonyloxy, and acyl groups.

When X or X_1 is a substituted alkoxy [-O-R_1], as hereinbefore defined, the R_1 group may be a (C_{2-6}) alkenyl, (C_{1-6}) alkoxy alkyl, (poly)hydroxy (C_{1-6}) alkyl, (poly)halo(C_{1-6}) alkyl, substituted or unsubstituted heteroaryl (C_{1-6}) alkyl, substituted mono- or di- amino (C_{1-6}) alkyl, substituted or unsubstituted heterocyclyl (C_{1-6}) alkyl, or N-(C_{1-6} alkyl)-N- heteroaryl-(C_{1-6})alkyl.

As used herein, the term "(poly)" refers to the optional substitution of more than one, such as (poly)haloalkyl would allow for more than one halogen, independently on the alkyl moiety, i.e., -CF_3.

Preferably the R_1 group is a C_{2-3} alkenyl, hydroxy C_{1-6} alkyl, (C_{1-6})alkoxy(C_{1-6})alkyl, (poly)halo(C_{1-6}) alkyl, (un)substituted (C_{1-6}) alkyl heteroaryl, (un)substituted (C_{1-6}) alkyl heterocyclyl, or N-(C_{1-6} alkyl)-N- pyridyl-(C_{1-6})alkyl. Preferably the heteroaryl is a pyridyl, or furanyl moiety. Preferably the heterocyclyl is a piperidine group.

More preferably R_1 is ethenyl, 2-ethanol, 3-propanol, -CH_2-O-CH_3, CH_2-furanyl, CH_2-furan-2-yl-5-nitro; CF_3, N-methyl-N-2-pyridylaminoethyl, N-piperidinylethyl, or 4-pyridylmethyl.

When X_1 is NR_2R_3, the R_2 and R_3 moieties are independently a (C_{1-6}) alkyl group or one of R_2 or R_3 may be a hydroxy (C_{1-6}) alkyl group. Preferably, both R_2 and R_3 are (C_{1-6}) alkyl, more preferably methyl; or one of R_2 R_3 is methyl and the other 2-ethanol.

Preferably the X_1 substitutents are selected from hydroxy, substituted and unsubstituted (C_{1-6})alkoxy, (C_{1-6})alkyl, oxy(C_{1-6})alkyl, cyano, chloro, fluoro, bromo, nitro, hydroxy(C_{1-6})alkyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6}) alkylsulphonyl, NR_2R_3, or (un)substituted heterocyclyl, or gem di(C_{1-6})alkoxy(C_{1-6})alkyl.

More preferably X_1 is methoxy, C(O)CH_3, methyl, cyano, chloro, fluoro, bromo, -CH(OCH_2CH_3)$_2$, nitro, -CH(O), N(CH_3)$_2$, SCH_3, S(O)CH_3, S(O)$_2CH_3$, -CH_2OH, piperidine, O-CF_3, hydroxy, ethenyloxy, 2-

hydroxyethoxy, N-(2-hydroxyethyl)-N-methylamino, 3-hydroxypropyloxy, azidoethoxy, N-methyl-N-pyridylaminoethoxy, piperidinylethoxy, pyridylmethyloxy, nitrofuranyl methyloxy, or furanylmethyloxy.

For the optional substituent groups X and X_1 wherein their respective members are also referred to as (un)substituted group, the optional substituents for said groups are independently substituted up to five times, preferably up to three times, from the same group listed herein under the X_1 term. For example, (un)substituted carbamoyl would allow the nitrogen atom to be mono- or di-substituted with a (C_{1-6})alkyl moiety; the (un)substitued heterocyclic would allow, for example, a piperidine ring to be substituted by a (C_{1-6})alkyl, or hydroxy moiety; an (un)substituted heteroaryl would allow for a furanyl ring to be substituted by a nitro group.

Preferred substituent groups (X_1) when B is an aryl group include, for example, halogen, cyano, (C_{1-6})alkyl, hydroxy(C_{1-6})-alkyl, oxo(C_{1-6})alkyl, gem di(C_{1-6})alkoxy(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{2-6})alkenoxy, hydroxy(C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, amino, mono- or di-(C_{1-6})alkylamino, acylamino, nitro, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, (C_{1-6})alkylcarbonyloxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})-alkylsulphonyl, sulphamoyl, mono- or di-(C_{1-6})alkylsulphamoyl, carbamoyl, mono- or di-(C_{1-6})alkylcarbamoyl and heterocyclyl.

Preferred substituents (X_1) when B is a heteroaryl group include, for example, halogen, (C_{1-6})alkyl, (C_{1-6})cycloalkyl, (C_{1-6})alkoxy, hydroxy(C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, amino, mono- or di-(C_{1-6})alkylamino, N-hydroxy(C_{1-6})alkyl N-(C_{1-6})alkyl amino, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, oxo, non-aromatic heterocyclyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl and (C_{1-6})alkylsulphonyl.

Preferred substituent (X_1) when B is a heterocyclyl group include, for example, halogen, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, (C_{1-6})alkoxy, hydroxy(C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, amino, mono- or di-(C_{1-6})alkylamino, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl and oxo.

When a substituent group, preferably in the $(B)_m$ term, has an acidic hydrogen arising from the presence in a heteroaryl ring of an NH moiety, for instance, when R^0 is pyrazolyl, the hydrogen may be replaced by a (X or X_1) substituent as hereinbefore defined. Preferably the substitutent is a (C_{1-6}) alkyl group.

As used herein, the term "alkyl" group or moiety referred to herein may be a straight or branched hydrocarbon chain, and may contain, for example, up to 12 carbon atoms, suitably up to 6 carbon atoms. The alkyl chain may be unsubstituted or substituted. In particular, the alkyl group or moiety may be an unsubstituted or substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, isobutyl or tert-butyl group. Examples of suitable optional substituents for any such alkyl group or moiety include the above-listed substituents for the $(A)_n$ term.

When used herein, the term 'aryl' includes, unless otherwise defined, phenyl or naphthyl.

When used herein, the term 'heterocyclyl' and 'heterocyclic' includes non-aromatic single or fused rings comprising up to four heteroatoms in each ring selected from oxygen, nitrogen and sulphur. Suitably, the heterocyclic ring comprises from 4 to 7, preferably from 5 to 6 ring atoms. A fused heterocyclic ring system may include aromatic carbocyclic and heteroaryl rings. Suitably the heterocyclic group is piperidinyl.

When used herein, the term 'heteroaryl' includes aromatic hetrocyclic containing rings and ring systems as is commonly defined in the art, such as by Katritzky et al., Handbook of Heterocyclic Chemistry, Pergamon Press, Oxford, England (1985). As defined therein, a heteroaromatic structure is based on the 6 π-electron system. These structure are related to and formally derived from benzene by successive replacement of one or two annular CH groups by trivalent or divalent heteroatom groups respectively. The overall patttern of filled bonding molecular orbitals is retained. Thus replacement of one CH group by O^+, S^+, or N gives the six-membered pyrylium, thiinium or pyridine systems, and replacement of two CH groups by O, S, or NH gives the five-membered furan, thiophene, or pyrrole. Multiple replacements are also possible with up to four

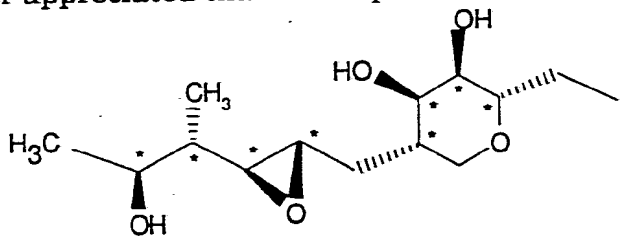
heteroatoms in five- and six-membered rings. Suitably the heteroaryl ring has 5 to 6 ring atoms in each ring. Prefered heteroaryl groups herein include, pyridyl, pyrimidinyl, furanyl, thienyl, thiazolyl, isoxazolyl, oxazolyl and pyrazolyl.

When used herein, the term "hydrocarbyl" may include groups having up to 18 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable groups include those listed under the $(A)_n$ term and the $(B)_m$ term groups which do not contain a heteroatom, i.e. cycloalkyl, cycloalkenyl and aryl.

It will be appreciated that another aspect of the present invention is in the many variations which can result from the point of attachment of the respective heteroaryl rings, such as in the 2-pyridyl, 3-pyridyl or 4-pyridyl moieties. Further where isomers of a heteroaryl exist, such as in a 1,3-pyrazolyl or 1,2- pyrazolyl, said isomers are also another aspect of the present invention.

When used herein, the term 'halogen' refers to fluorine, chlorine, bromine or iodine. Preferably, the halogen is fluoro, chloro or bromo.

It will be further appreciated that in compounds of formula (I), the moiety:



will have the same relative and absolute stereochemistry at each of the chiral centres (indicated by *) as that of corresponding moiety in mupirocin i.e. [2S, 3R, 4R, 5S] about the tetrahydropyran ring and [2S, 3S, 4S, 5S] in the 5-(2,3-epoxy-5-hydroxy-4-methylhexyl) sidechain of the tetrahydropyran ring.

The compounds of the present invention may exist in the forms shown in formulae (IA), (IB) or (IC), the three forms being in equilibrium. It will be appreciated that the compounds of formulae (IA), (IB), and (IC) are interrelated by keto-enol tautomerism, with formula (IA) representing the keto tautomer and formula (IB) and (IC) representing the two possible

enol tautomers. References hereinafter to 'formula (I)' encompass all three forms unless the context requires otherwise.

It will be appreciated that in compounds of formula (I), the group R^o may contain one or more chiral centres. The present invention encompasses all such resultant isomeric possibilities.

Since the compounds of formula (I) of the present invention are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise, or are recrystallised, from organic solvents. solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Examples of compounds within the scope of this invention include the following:

3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-(2,4-dioxo-4-phenyl-but-1-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)-but-1-yl]-5S-(2S,3S,epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

2S-[4-(4-Acetylphenyl)-2,4-dioxobut-1-yl]-3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(4-dimethylaminophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-(2,4-dioxo-4-(furan-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-2-yl)but-1-yl]5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-hydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(4-cyanophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(4-chlorophenyl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(4-diethoxymethylphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(4-dioxo-4-(4-formylphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran.

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphinylpyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphonylpyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-hydroxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-nitrothien-4-yl)but-1-yl]-5S-(2S,3S-

epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-methoxyfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)-pyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methyl-2-methylthioimidazol-4-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylsulphinyl-phenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylsulphonyl-phenyl)-but-1-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-cyanophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-trifluoromethoxy-phenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-hydroxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(but-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-hydroxyethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(3,4-difluorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-N-(2-hydroxyethyl)-N-methylaminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(4-hydroxypiperidin-1-yl)pyrid-5-yl)-but-1-yl]-5S-[2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(3-hydroxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxythiazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(cyclohexen-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-

(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-hydropyran;

3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-(3,5-dioxo-1-phenylhex-1-yn-6-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-N-methyl-N-2-pyridylamino-ethoxy}phenyl)but-1-yl-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-piperidinylethoxy}phenyl)but-1-yl-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{4-pyridylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{5-nitrofuran-2-ylmethyloxy}phenyl) but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran; and

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{furan-2-ylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-6S-hydroxy-4S-methylhexyl)tetrahydropyran.

Preferred compounds of the instant invention are:

3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)-but-1-yl]-5S-(2S,3S,epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

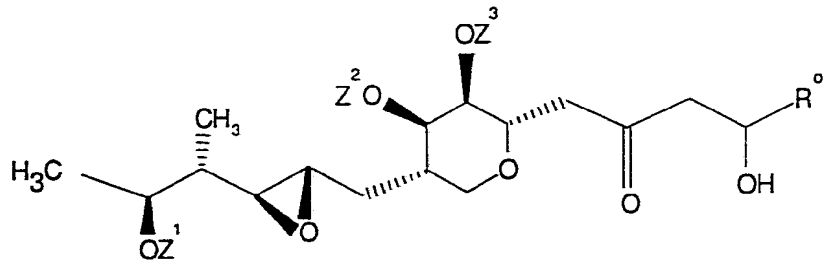
3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-hydroxyethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran; and

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran.

Compounds of the present invention may be prepared by methods known for the preparation of β-diketones. Some of these processes will be more

appropriate than others.

Suitably, compounds of formula (I) may be prepared by a process which comprises treating a compound of formula (II):



(II)

in which Z^1, Z^2 and Z^3 are the same or different and each is hydrogen or a hydroxyl-protecting group, and R^0 is as hereinbefore defined;

with an oxidising agent which converts a β-hydroxyketone into a β-diketone;

and thereafter, and if necessary, removing any hydroxyl-protecting groups.

Suitably such oxidising agents include, for example, activated manganese dioxide, 2,3-dichloro-5,6- dicyano-1,4-benzoquinone (DDQ), chromium trioxide, pyridinium dichromate, pyridinium chlorochromate, dimethylsulphoxide/trifluoroacetic anhydride, dimethylsulphoxide/oxalyl chloride, ruthenium tetroxide, and tetra-n-propylammonium perruthenate.

Suitably, the oxidation reaction is effected in a organic solvent such as, for example, dioxan, acetonitrile, tetrahydrofuran, ether, carbon tetrachloride, chloroform, dichloromethane, benzene or toluene and at a temperature which is preferably in the range from -20° to 100°C.

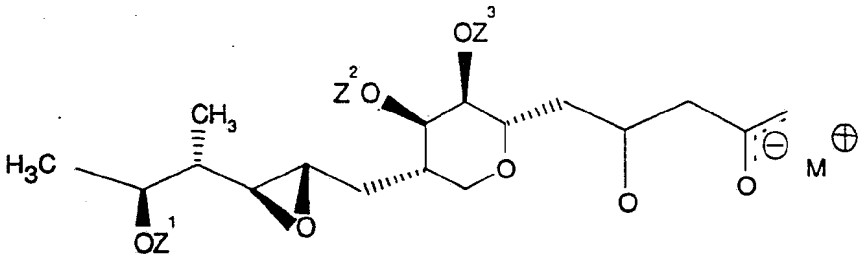
Preferably, the compounds of Formula (I) wherein $(A)_n$ is an alkenyl or alkenyl moiety in which the double or triple bond is in a conjugated or non-conjugated system with the rest of the molecule are made according to

the process of Formula (II) as noted above. Alternatively, under carefully controlled conditions the process of Formula (VI) as hereinbelow defined, may also be used.

Compounds of formula (II) are novel and useful intermediates for the preparation of compounds of formula (I).

Accordingly, a further aspect of the invention also provides a compound of formula (II) as hereinbefore defined.

Compounds of formula (II) may be prepared by a process which comprises treating a compound of formula (III):



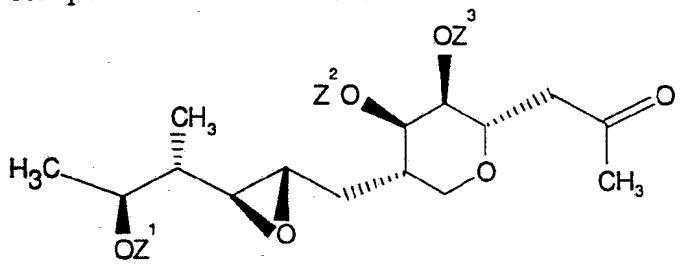
(III)

in which Z^1, Z^2 and Z^3 are as hereinbefore defined and M^+ is a metal such as lithium, with an aldehyde of formula (IV):

$$R^0CHO \qquad (IV)$$

in which R^0 is as hereinbefore defined and thereafter, and if necessary, removing any hydroxyl-protecting groups.

A compound of formula (III) may be obtained by treating a ketone compound of formula (V):



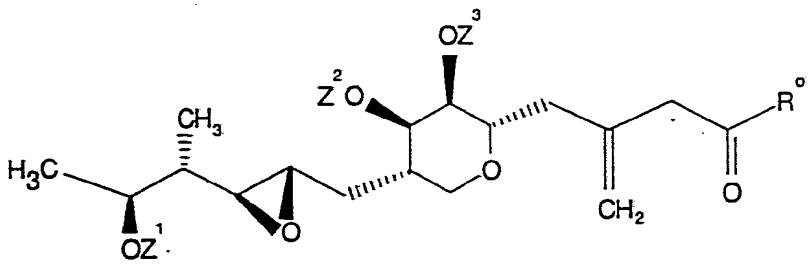
(V)

in which Z^1, Z^2 and Z^3 are as hereinbefore defined, with a suitable enolising agent such as, for example, lithium diisopropylamide.

It will be appreciated that in practice, the compound of formula (III) may be generated in situ, prior to the treatment thereof with a compound of formula (IV).

The preparation of a compound of formula (V) is described in GB 1 587 58 (to Beecham Group plc).

In a further aspect, the present invention provides a second process for preparing a compound of formula (I) as hereinbefore defined, which process comprises treating a compound of formula (VI):



(VI)

in which Z^1, Z^2, Z^3 and R^o are as hereinbefore defined, with a reagent capable of converting a terminal methylene-substituent to an oxo-substituent and thereafter, and if necessary, removing any hydroxyl-protecting groups.

Suitable reagents for effecting such a conversion include ozone and osmium tetroxide, each of which forms an intermediate which may then be converted to the compound of formula (I). Alternative reagents useful in the conversion herein may be found in Harrison et al, Compendium of Organic Synthetic Methods, Wiley-Interscience (1971).

Ozonolysis may be effected under conditions conventionally used for such a reaction. Thus the reaction may be effected at a low temperature, for instance about -70°, in the presence of a suitable solvent such as dichloromethane. The intermediate ozonide thus formed may be

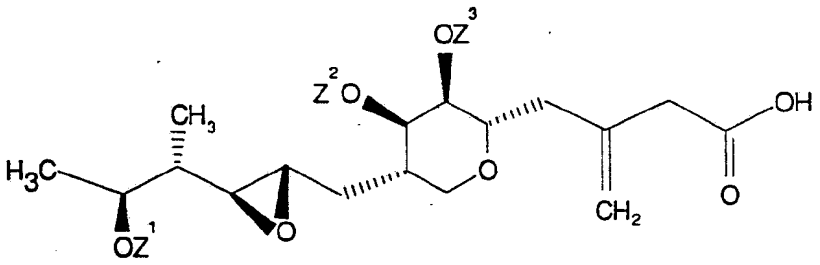
conveniently decomposed by an agent conventionally used for such a task, of which triphenyl phosphine is especially preferred.

Alternatively, the compound of formula (VI) may be treated with osmium tetroxide, according to the procedure described by V. Van Rheenen, R.C. Kelly and D.Y. Cha, Tetrahedron Lett, 1976, 1973. Preferably a catalytic quantity of osmium tetroxide is employed, in the presence of a tertiaryamine oxide catalyst such N-methylmorpholine N-oxide, in a solvent such as aqueous tetrahydrofuran, to give an intermediate 1,2-diol which may then be treated with an oxidising agent such as sodium periodate to give the compound of formula (VI).

Compounds of formula (VI) are novel and useful intermediates for preparing of compounds of formula (I).

Accordingly, a further aspect of the invention also provides a compound of formula (VI) as hereinbefore defined.

Suitably, compounds of formula (VI) may be prepared by a process which comprises treating the acid of formula (VII) or an activated derivative thereof:



(VII)

in which Z^1, Z^2 and Z^3 are the same or different and each is hydrogen or a hydroxyl-protecting group,

with an organometallic reagent;

and thereafter, and if necessary, removing any hydroxyl-protecting groups.

Suitable organometallic reagents include:

(i) a Grignard reagent of the formula R^0MgX in which R^0 is as defined with respect to formula (I) and X represents chlorine, bromine or iodine, which reaction may optionally be carried out in the presence of copper(I) iodide as catalyst;

(ii) an organolithium reagent of formula R^0Li in which R^0 is as defined with respect to formula (I);

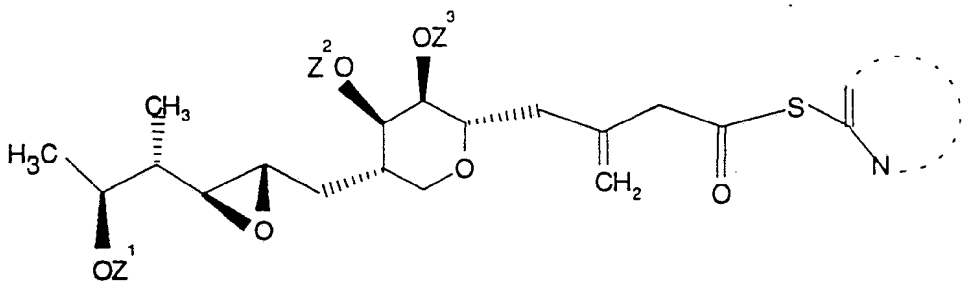
(iii) an organomanganous reagent of the formula R^0MnCl in which R^0 is as defined with respect to formula (I); and

(iv) an organocerium reagent $R^0Li\text{-}CeX_3$, in which R^0 is as defined with respect to formula (I) and X represents chlorine, bromine or iodine.

The reaction with the organometallic reagent may be conveniently carried out in an ethereal or hydrocarbon solvent, the choice of which is dependent upon the specific requirements of the organometallic reagent. Preferably, the Grignard reagent is generated and used in diethyl ether or tetrahydrofuran.

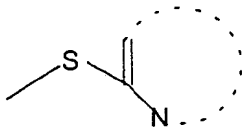
The reaction is generally carried out in an inert atmosphere such as argon or nitrogen and at ambient temperature or below. The period for which the reaction is allowed to proceed depends upon the particular starting materials employed. The course of the reaction may be followed by conventional methods such as thin layer chromatography and the reaction may be terminated when an optimum quantity of product is present in the reaction mixture.

Suitable activated derivatives of the acid of formula (VII) include thio-esters of formula (VIII):



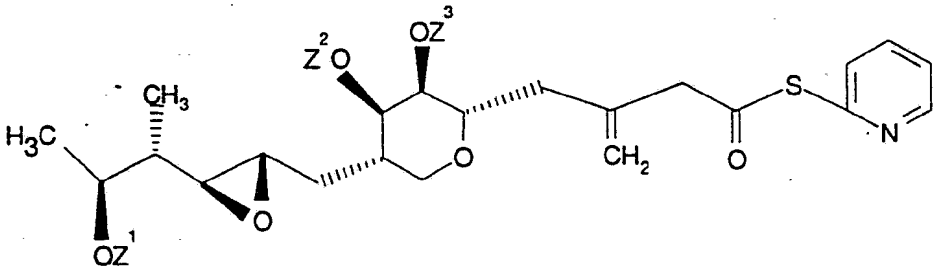
(VIII)

in which Z^1, Z^2 and Z^3 are as hereinbefore defined and the moiety:



represents a 5- or 6-membered heterocyclic ring which may contain in addition to the nitrogen atom, one or two further heteroatoms selected from oxygen, nitrogen and sulphur and which may be substituted or fused to a benzene ring which may itself be substituted.

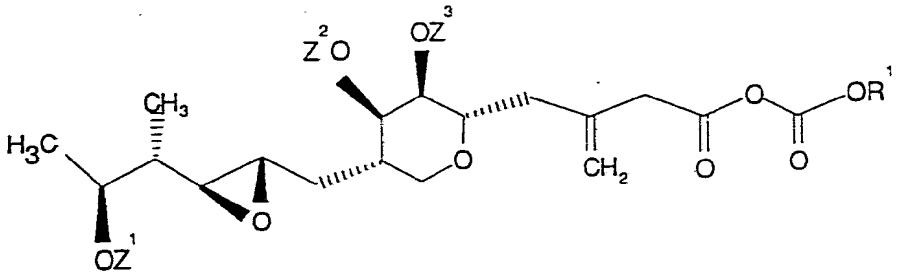
Preferred thio-esters are of formula (VIIIa):



(VIIIa)

in which Z^1, Z^2 and Z^3 are as hereinbefore defined.

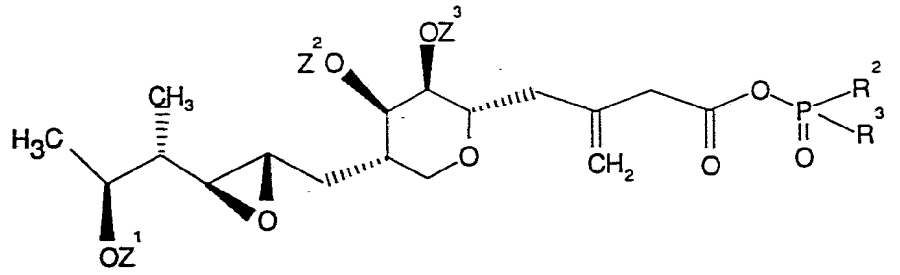
Other suitable activated derivatives of the acid of formula (VII) include mixed anhydrides of the formula (IX):



(IX)

in which Z^1, Z^2, and Z^3 are as hereinbefore defined, and R^1 is (C_{1-6})alkyl;

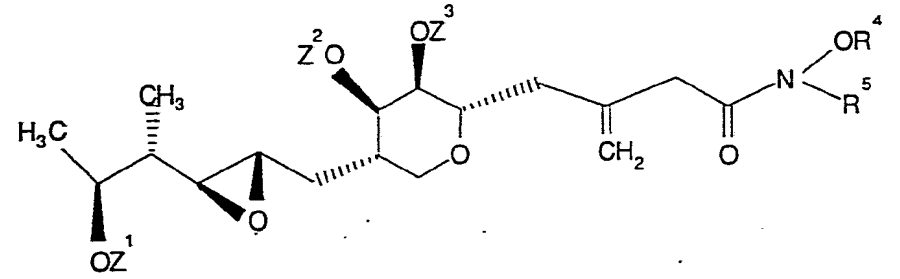
and of the formula (X):



(X)

in which Z^1, Z^2, and Z^3 are as hereinbefore defined, and R^2 and R^3 are the same or different and each denotes an aryl group, for instance phenyl, or a (C_{1-6})alkoxy group, for instance ethoxy.

Further suitable activated derivatives of the acid of formula (VII) include amides of the formula (XI):

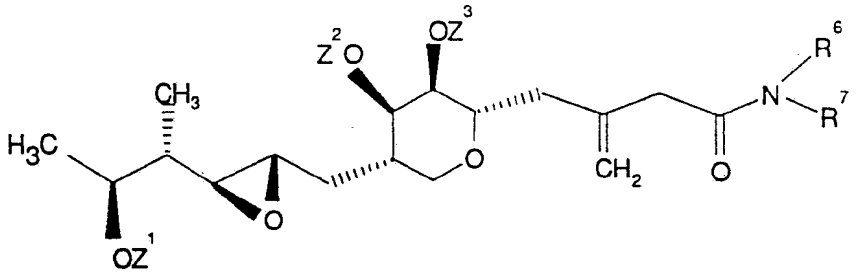


(XI)

in which Z^1, Z^2 and Z^3 are as hereinbefore defined, R^4 and R^5 are the

same or different, and each is (C_{1-6})alkyl, preferably methyl, or the substituents R^4 and R^5 form a (C_{2-7})alkylene chain and;

amides of the formula (XII):



(XII)

in which Z^1, Z^2, and Z^3 are as hereinbefore defined and R^6 and R^7, together with the nitrogen atom to which they are bonded, form an imidazolyl or triazolyl ring.

The reaction of an N-methoxy-N-methylamide compound with an organolithium or a Grignard reagent to form a ketone is described by Nahm and Weinreb in Tetrahedron Lett, 1981, 3815. The reaction of an α,β-unsaturated acid or its imidazolyl derivative with a Grignard reagent is described in Chem. Ber., 1965, 95 1284.

Suitably a thio-ester of formula (VIII) is treated with an organomanganous reagent of formula R^0MnCl, as hereinbefore defined.

Suitably an amide of formula (XI) or (XII) is treated with an organolithium reagent of formula R^0Li as hereinbefore defined:

Suitable organometallic reagents may be prepared according to conventional procedures.

Suitable organomanganous reagents of the formula R^0MnCl may be conveniently prepared by addition of an organolithium reagent R^0Li to a solution of manganous chloride and lithium chloride in dry THF, or a suspension of anhydrous manganous chloride in dry THF. An excess of R^0MnCl is preferably employed. Alternatively, a Grignard reagent may

be used in place of the organolithium reagent, to generate the organomanganous reagent R^0MnCl.

Other organomanganous reagents which may be used instead of R^0MnCl include:

(i) $(R^0)_3MnLi$ or $(R^0)_3MnMgX$ in which X is as hereinbefore defined, as described in Synthetic Communications, 1979, 9, 639;

(ii) R^0MnI in ether; as described in Synthetic Communications, 1979, I, 639; and

(iii) R^0MnBr in ether, as described in Tetrahedron Lett., 1976, 3155.

As in the case of R^0MnCl, the above organomanganous reagents may be prepared in situ when required.

Organocerium reagents may be generated in situ by treatment of an organolithium compound of the formula R^0Li, in which R^0 is as hereinbefore defined, with cerium (III) halide, by analogy with the procedure described by Imamoto et al; J.Chem. Soc., Chem. Commun, 1982, 1042.

The activated derivatives of compounds of formula (VI) may be prepared from the compounds of formula (VI) by standard methodology.

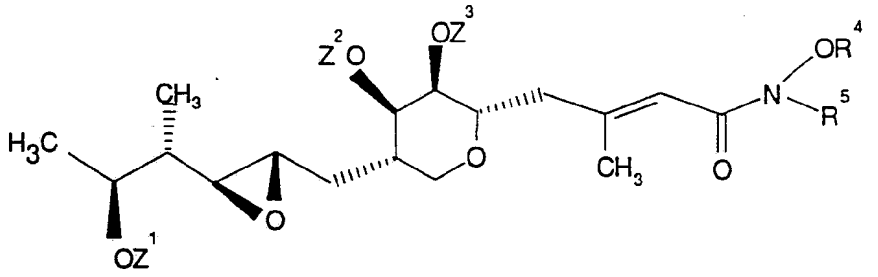
Compounds of formula (VII) may be obtained by treating the protected methylester of monic acid with a base such as lithium diisopropylamide, as described by Crimmin et at, J. Chem. Soc., Perkin Trans I, 1985, 549, followed by ester hydrolysis.

Advantageously, a compound of formula (VI) may be prepared by treating a compound of formula (XI) in which R^4 and R^5 each is methyl with an organometallic reagent which is preferably an organolithium reagent of the formula R^0Li.

Compounds of formula (XI) are novel and useful intermediates in the preparation of compounds of formula (VI).

Accordingly, a further aspect of the invention provides compounds of formula (XI) as hereinbefore defined.

Compounds of formula (XI) may also be obtained by a process which comprises treating a compound of formula (XIII):



(XIII)

in which Z^1, Z^2, Z^2, R^4 and R^5 are as hereinbefore defined, with a strong non-nucleophilic base such as, for example, lithium diisopropylamide, followed by quenching with a mild proton source such as ammonium chloride.

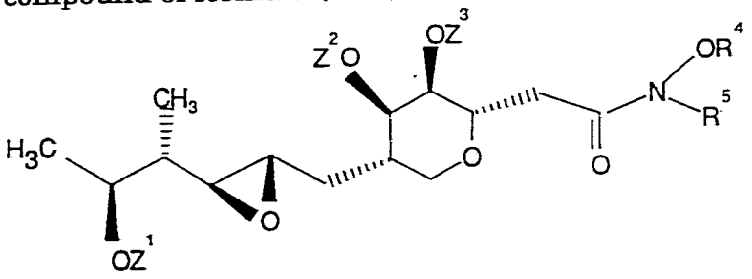
Compounds of formula (XIII) are novel and useful intermediates for the preparation of compounds of formula (XI).

Accordingly, a further aspect of the invention provides a compound of formula (XIII) as hereinbefore defined.

Compounds of formula (XIII) may be prepared from monic acid by initial conversion thereof to an activated derivative, for instance a mixed anhydride such as that formed with iso-butylchloroformate, followed by subsequent treatment with an amine $HN(OR^4)R^5$ in which R^4 and R^5 are as hereinbefore defined, or a salt thereof; under standard conditions, for instance, with dichloromethane as the reaction solvent, at about 0°C for 2h; and thereafter and if required, introducing any hydroxyl-protecting groups that may be subsequently required.

In a further aspect, the present invention provides a third process for preparing a compound of formula (I) which process comprises treating a

compound of formula (XIV):



(XIV)

in which Z^1, Z^2, Z^3, R^4 and R^5 are as hereinbefore defined, with a compound of formula (XV):

$$R^oCOCH_2^-$$

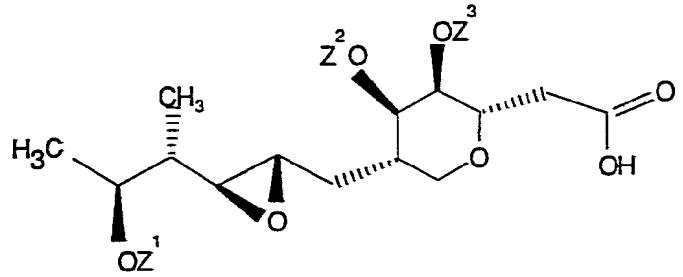
(XV)

in which R^o is as hereinbefore defined and thereafter, and if necessary, removing any hydroxyl-protecting groups.

Compounds of formula (XIV) are novel and useful intermediates for the preparation of compounds of formula (I).

Accordingly, a further aspect of the invention provides a compound of formula (XIV) as hereinbefore defined.

Compounds of formula (XIV) may be prepared from the corresponding acids of formula (XVI):



(XVI)

in which Z^1, Z^2 and Z^3 are as hereinbefore defined, by initial conversion thereof to an activated derivative, for instance a mixed anhydride such as that formed with iso-butylchloroformate, followed by subsequent

treatment with an amine $HN(OR^4)R^5$, in which R^4 and R^5 are as hereinbefore defined, or a salt thereof, under standard conditions, for instance, with dichloromethane as the reaction solvent, at about 0°C for 2h.

Compounds of formula (XVI) are novel and useful intermediates for the preparation of compounds of formula (I).

Accordingly, a further aspect of the invention provides a compound of formula (XVI), as hereinbefore defined.

Compounds of formula (XVI) may be prepared from compounds of formula (V), as hereinbefore defined, and in which the hydroxyl groups are protected, preferably as a silylether, by initial conversion thereof to the enol form followed by ozonoloysis and subsequent decomposition of the intermediate ozonide using, for instance, dimethyl sulphide.

Compounds of formula (I) may be obtained from other compounds of formula (I) by suitable manipulation of the substituents present in the group R^o according to conventional methodology. For instance, an alkylthio substituent may be converted to an alkyl sulphinyl or an alkylsulphonyl substitutent by treatment thereof with a conventional oxidising agent such as m-chloroperbenzoic acid.

When used herein, the term 'hydroxyl-protecting group' refers to any such group known in the art which may be removed without disruption of the remainder of the molecule. Suitable hydroxyl-protecting groups include those described in 'Protective Groups in Organic Synthesis', T.W. Greene, Wiley-Interscience, New York 1981.

The hydroxyl groups of the compounds of formulae (II), (III), (V) to (XIV) and (XVI) may be protected at any stage of the above processes, using conventional methods. The hydroxyl-protecting group may be removed by methods known in the art, including enzymatic methods.

Particularly suitable hydroxyl-protecting groups are silyl groups since these are readily removed under mild conditions. Such groups are introduced using conventional silylating agents, including halosilanes and silazanes, of the formulae below:

L_3SiY

L_2SiY_2

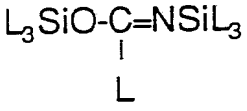
L_3SiNL_2

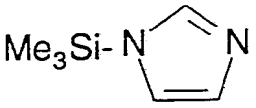
$L_3SiNHSiL_3$

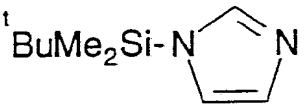
$L_3SiNHCOL$

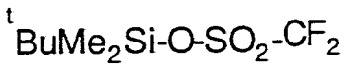
$L_3SiNHCONHSiL_3$

$LNHCONHSiL_3$



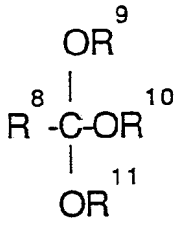






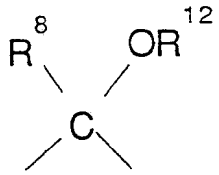
wherein Me denotes methyl and ^tBu denotes t-butyl, Y is halogen and each group L is independently selected from hydrogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, aryl or aryl(C_{1-4})alkyl. A preferred silyating agent is trimethylsilyl chloride. Particularly suitable protecting groups are trimethylsilyl, triethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl groups. Preferred protecting groups are trimethylsilyl groups because of their ease of removal.

The glycol function of the compounds of formulae (II), (III), (V) to (XIV) and (XVI)may be protected by forming a cyclic derivative using a compound of formula (XVII):



(XVII)

wherein R^8 is hydrogen or (C_{1-6})alkyl and each of R^9, R^{10} and R^{11} is (C_{1-6})alkyl. In the cyclic derivative Z^1 and Z^2 together are a moiety:



in which R^8 is as hereinbefore defined and R^{12} is (C_{1-6})alkyl.

Suitably R^8 is hydrogen, methyl, ethyl, n- or iso-propyl; most suitably it is hydrogen. The groups R^9, R^{10} and R^{11} are suitably methyl, ethyl, n- or iso-propyl, or n-, iso-, sec- or t-butyl; most suitably methyl.

Similarly the hydroxyl groups of a compound of formula (I) may be protected prior to conversion to a further compound of formula (I) as described above.

In each case the hydroxyl-protecting groups described above may be removed by mild acid hydrolysis followed by alkaline hydrolysis, for instance, as described by J.P. Clayton, K. Luk and N.H. Rogers, in 'Chemistry of Pseudomonic Acid, Part II', J.C.S. Perkin Trans. I, 1979, 308.

The compounds of this invention are useful in therapy, in particular for the treatment of bacterial and mycoplasma-induced infections in non-human and human animals, such as the treatment of respiratory tract infections, otitis, meningitis, skin and soft tissue infections in human animals, mastitis in cattle, and respiratory infections in non-human animals such as pigs and cattle.

The compounds of this invention are active against both Gram negative and Gram positive organisms, including Haemophilus, for instance H.influenzae Q1; Branhamella,for instance B.Catarrhalis 1502; Streptococci, for instance S.pyogenes CN10 and S.pneumonia PU7; and Staphylococci, for instance S.aureus Oxford, Legionella, for instance L. pneumophila; and against mycoplasma. In addition, compounds of the present invention are active against Staphylococci organisms such as S. aureus and S. epidermis which are resistant, including multiply resistant, to other anti-bacterial agents, for instance macrolides; aminoglycosides; lincosamides; and β-lactams, such as, for example methicillin.

The compounds of this invention are also active against mycoplasma-induced infection, in particular Mycoplasma fermentans, which has been implicated as a co-factor in the pathogenesis of AIDS.

Accordingly in a further aspect, the present invention provides a method of treating humans infected with M. fermentans, in particular humans also infected with HIV, which method comprises treating humans in need of such therapy with an anti-mycoplasmal effective amount of a compound of formula (II).

This invention also provides a pharmaceutical or veterinary composition which comprises a compound of formula (I) (hereinafter referred to as the 'drug') together with a pharmaceutically or veterinarily acceptable carrier or excipient.

The compositions may be formulated for administration by any route, for instance, by topical, parenteral or oral administration and would depend on the disease being treated. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical or sterile parenteral suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous

vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

For topical application to the skin the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as 'Harry's Cosmeticology' published by Longman, and the British Pharmacopoeia.

Suppositories will contain conventional suppository bases, e.g. cocoa-butters or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the drug and a sterile vehicle. The drug, depending on the vehicle and concentration used, can be suspended in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability thereof the composition may be frozen after filling into the vial and water removed under vacuum. The dry lypophilized powder is then sealed in the vial. The drug can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the drug.

For topical application to the ear, the drug may be made up into a suspension in a suitable liquid carrier, such as water, glycerol, diluted ethanol, propylene glycol, polyethylene glycol or fixed oils.

For topical application to the eye, the drug is formulated as a suspension in a suitable, sterile aqueous or non-aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edetate; preservatives including bactericidal and fungicidal agents, such as phenylmercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage employed for compositions administered topically will, of course, depend on the size of the area being treated. For the ears and eyes each dose will typically be in the range from 10 to 100 mg of the drug.

Veterinary compositions for intramammary treatment of mammary disorders in animals, especially bovine mastitis, will generally contain a suspension of the drug in an oily vehicle.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the drug,depending on the method of administration. Where the compositions are in unit dose form, each dosage unit will preferably contain from 50-500 mg of the drug. The dosage as employed for adult human treatment will preferably range from 100 mg to 3 g, per day, for instance 250 mg to 2 g of the drug per day, depending on the route and frequency of administration.

Alternatively, the drug may be administered to non-human animals as part of the total dietary intake. In this case the amount of drug employed may be less than 1% by weight of the diet and in preferably no more than 0.5% by weight. The diet for animals may consist of normal foodstuffs to which the drug may be added or the drug may be included in a premix for admixture with the foodstuff. A suitable method of administration of the drug to a non-human animal is to add it to the non-human animal's drinking water. In this case a concentration of the drug in the drinking water of about 5-500 μg/ml, for example 5-200 μg/ml, is suitable.

The present invention further provides a method for treating the human or non-human animal which method comprises administering a compound of formula (I) as hereinbefore defined, to a human or non-human animal in need of such therapy.

Alternatively, a pharmaceutical composition as hereinbefore described may be employed in the treatment.

In particular aspects of the treatment, there are provided methods for treating bacterial infections and mycoplasma-induced infections of human or non-human animals, especially respiratory infections in human or

non-human animals.

The present invention also provides a compound of formula (I) as hereinbefore defined for use in therapy.

The present invention also provides a compound of formula (I) as hereinbefore defined for use in the manufacture of a medicament for anti-bacterial therapy or mycoplasma-induced infections.

The following Examples illustrate the invention, but are not intended to limit the scope in any way.

The Examples hereinafter are named according to the IUPAC convention. For the H nmr data, however, the numbering system is derived from monic acid viz:

Preparation of N-methoxy-N-methyl 6,7,13-tris-trimethylsilyl monamide

N,O-dimethyl hydroxylamine hydrochloride (1.95grams (hereinafter g.), 20milimoles (hereinafter mmoles)) was dissolved in dichloromethane/aqueous sodium hydroxide (20milliters (hereinafter ml:10ml, 2.5Molar (hereinafter M)). The aqueous layer was re- extracted with dichloromethane (10ml) and the combined organic layers washed with saturated brine (5ml). The organic layer was dried ($MgSO_4$) and added to monic acid isobutyl carbonic anhydride (10mmol)*. After stirring at 20°C for 1 hour (hereinafter h) the reaction mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen chloride and brine. The combined aqueous solutions were extracted with ethyl acetate, and the combined organic solutions dried ($MgSO_4$) and concentrated to give the amide, 3.0g.

This was taken up in tetrahydrofuran (50ml) and treated with triethylamine (8.4ml, 60mmol) and chlorotrimethyl silane (6.3ml, 50mmol). After 10 minutes a catalytic amount of 4-DMAP was added.

After 2h at room temperature the reaction was diluted with diethyl ether, filtered, and the filtrate evaporated. The residue was taken up in hexane, refiltered, and washed with water and brine. After drying and

evaporation the residue was taken up in hexane (20ml) and allowed to crystallise at 0 to -20°C, to give the required product as a colourless crystalline solid, 34.0g, 50%, mp 78-79°C.

*Monic acid isobutyl carbonic anhydride was obtained by treating monic acid with iso-butylchloroformate and triethylamine in tetrahydrofuran at from -5 to 20°C for about 30 min.

Example 1

3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) Deconjugation of N-Methoxy-N-methyl-6,7,13-tristrimethylsilylmonamide

A solution of N-methoxy-N-methyl-6,7,13-tristrimethylsilylmonamide (1.2g, 2mmol) in dry THF (20ml) under argon at -70°C was sequentially treated with diisopropylamine (0.03ml, 0.2mmol) and a solution of t-butyllithium (1.7M, 1.4ml, 2.4mmol) in hexane. After 30min the reaction mixture was quenched with saturated ammonium chloride. Ethyl acetate was added and the organic phase was washed with water, brine, then dried and evaporated to give a 4:1 mixture of the deconjugated$^+$ and conjugated* monamides in quantitative yield. δ_H ($CDCl_3$) inter alia 4.93 (4/5H, s, 15-H$^+$), 5.03 (4/5H, s, 15-H$^+$) 6.18 (1/5H, s, 2-H*).

b) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-yl]methylprop-2-ene-1-yl 4-methoxyphenyl ketone

A solution of p-bromoanisole (0.75ml, 6mmol) in THF (20ml) at -70°C under argon was treated with a solution of n-butyllithium (1.5M, 4ml, 6mmol) in hexane. After 30min the mixture was treated with a solution of the mixture from 1a (1.2g, 2mmol) in THF (5ml). After a further 30min saturated ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$),evaporated and chromatographed on silica eluting with ethyl

acetate/hexane mixtures to give material containing the title compound (543mg); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 6.9Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.87 (3H, s, Ar-OMe), 4.89 (1H, s, 15-H), 5.06 (1H, s, 15-H), 6.92 (2H, d, J 8.4Hz, 3',5'-H_2), 7.97 (2H, d, J 8.7Hz, 2',6'-H_2).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)-but-1-yll-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydrofuran

A solution of the ketone from 1b (630mg, 0.8mmol) in dichloromethane (25ml) at -70°C was ozonolysed until a blue colour persisted. Argon was then passed through the mixture. Triphenylphosphine (124gmg 0.47mmol) was added and the mixture warmed to room temperature. The mixture was evaporated to low volume and chromatographed on silica eluting with ethyl acetate/hexane mixtures to give the title compound (370mg, 70%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.86 (3H, s, OMe), 6.20 (1H, s, 2-H), 6.93 (2H, d, J 8.7Hz, 3',5'-H_2), 7.95 (2H, d, J 8.7Hz, 2',6'-Hz). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxyphenyl)-but-1-yll-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran

A solution of the ketone from 1c (360mg, 0.54mmol) in methanol (10ml) was treated with dimethylaminopyridine dihydrochloride (3mg). After 30min the reaction mixture was diluted with dichloromethane, washed with sodium hydrogen carbonate solution, dried and evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound (175mg, 74%); ν_{max} (KBr) 3435, 1603cm^{-1}; λ_{max} (EtOH) 324nm (ε_m 18,430); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.1Hz, 14-H_3), 3.86 (3H, s, Ar-OMe), 6.20 (1H, s, 2-H), 6.92 (2H, d, J 9.8Hz, 3',5'-H_2), 7.87 (2H, d, J 9.8Hz, 2',6'-H_2). δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.7 (C-9), 39.7 (C-8), 42.5 (C-4), 42.8 (C-12), 55.5 (OMe), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 69.1 (C-6), 70.3 (C-13), 71.3 (C-7), 73.9 (C-5), 96.5 (C-2), 114.0 (C-3'5'), 126.9 (C-1'), 129.3 (C-2',6'), 163.3 (C-4'), 183.0 (C-3), 193.1 (C-1). M/Z (FAB) MH± 437. The ^1H nmr spectrum indicatd that the title compound

was essentially in the enolic form.

Example 2

3R,4R-Dihydroxy-2S-(2,4-dioxo-4-phenyl-but-1-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-yl]methylprop-2-en-1-yl phenyl ketone

A solution of the products from 1a (600mg, 1mmol) in THF (20ml) under argon at -70°C was treated with a solution of phenyllithium in ether (2M, 1.5ml, 3mmol). After 30min the reaction was worked up as in 1b to give material containing the title compound (300mg); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz), 1.19 (3H, d, J 6.3Hz, 14-H_3), 4.91 (1H, s, 15-H), 5.08 (1H, s, 15-H), 7.40-7.60 (3H, m), 7.44-8.05 (2H, m).

b) 3R,4R-Bistrimethylsilyloxy-2S-(2,4-dioxo-4-phenyl-but-1-yl)-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrhydropyran

The material from 2a (300mg, 0.47mmol) was converted to the title compund (182mg, 61%) using the method described in 1c. δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 6.27 (1H, s, 2-H), 7.43-7.60 (3H, m), 7.82-7.95 (2H, m). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-(2,4-dioxo-4-phenyl-but-1-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 1d, the ketone from 2b (180mg, 0.28mmol) was deprotected to give the title compound (53mg, 47%); υ_{max} (KBr) 3422, 1609, 1570cm^{-1}; λ_{max} (EtOH) 312nm (ε_m 13,620), 248 (5140); δ_H ($CDCl_3$), inter alia 1.06 (3H, d, J 6.9Hz, 17-H_3), 1.29 (3H, d, J 6.2Hz, 14-H_3), 6.28 (1H, s, 2-H), 7.36-7.64 (3H, m), 7.83-7.98 (2h, m); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.6 (C-8), 42.8 (C-4), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 69.0 (C-13), 71.3 (C-7), 73.8 (C-5), 97.5

(C-2), 127.1 (C-3'5'), 128.7 (C-2',6'), 132.6 (C-4'), 134.3 (C-1'), 182.3 (C-3), 196.0 (C-1); (Found: M$^+$ 406.1991. $C_{22}H_{30}O_7$ requires M 406.1992). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

Example 3

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)-but-1-yl]-5S-(2S,3S,epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-yl]methylprop-2-ene-1-yl 2-methoxy pyrid-5-yl ketone

Using the method described in 1b and on the same scale, 2-methoxy-5-bromopyridine (1.13g, 6mmol) was reacted to give material containing the title compound (470mg); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.00 (3H, s, OMe), 4.90 (1H, s, 15-H), 15.08 (1H, s, 15-H), 6.77 (1H, d, J 8.8Hz, 3'-H), 8.16 (1H, dd, J 2.3, 8.6Hz, 4'-H), 8.82 (1H, d, J 2.2Hz, 6'-H).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 1c, the material from 3a (470mg, 0.71mmol) was converted to the title compound (330mg, 70%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 4.00 (3H, s, OMe), k6.18 (1H, s, 2-H), 6.79 (1H, d, J 8.7Hz, 3'-H), 8.06 (1H, dd, J 2.3, 8.7Hz, 4'-H), 8.72 (1H, d, J 2.7Hz, 6'-H). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 1d, the material from 3b was deprotected to give the title compound (100mg, 46%); ν_{max} (KBr) 3503, 3428, 1603,

1494cm^{-1}; λ_{max} (EtOH) 315.5nm (ε_m 17,120); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 4.00 (3H, s, OMe), 6.19 (1H, s, 2-H), 6.80 (1H, d, J 9.8Hz, 3'-H), 8.05 (1H, dd, J 2.4, 9.8Hz, 4'-H), 8.72 (1H, d, J 2.4Hz, 6'-H); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.7 (C-9), 39.7 (C-8), 42.2 (C-4), 42.9 (C-12), 54.3 (C-10), 55.7 (C-11), 61.3 (OMe), 65.7 (C-16), 69.0 (C-6), 70.3 (C-13), 71.4 (C-7), 73.9 (C-5), 96.8 (C-2), 111.0 (C-3'), 124.0 (C-5'), 137.2 (C-4'), 147.6 (C-6'), 166.7 (C-2'), 181.9 (C-3), 194.0 (C-1); (Found: M^+ 437.2048. $C_{22}H_{31}NO_8$ requires M^+ 437.2050).

Example 4

2S-[4-(4-Acetylphenyl)-2,4-dioxobut-1-yl]-3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

To a solution of the trimethylsilylenol ether of p-bromoacetophenone (1.63g, 6mmol) in THF (20ml) under argon at -70°C was added dropwise a solution of n-butyllithium (1.5M, 4ml, 6mmol) in hexane. After 30min a solution of the mixture from 1a (1.2g, 2mmol) in THF (5ml) was added. After 30min saturated ammonium chloride was added and the mixture extracted with ethyl acetate. The organic phase was washed with brine, dried and evaporated. The residue was filtered through silica eluting with 20% (v/v) ethyl acetate/hexane. The filtrate was evaporated then dissolved in methanol (20ml) and treated with dimethylaminopyridine dihydrochloride (3mg). After 20min the mixture was diluted with ethyl acetate washed with sodium hydrogen carbonate, brine then dried and evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave material (330mg) which was a 2:1 mixture of deconjugated* and conjugate$^+$ ketones [δ_H ($CDCl_3$) 5.00 (2/3H, s, 15-H*), 5.18 (2/3H, s, 15-H*), 6.83 (1/3H, s, 2-H$^+$)].

This material was dissolved in dichloromethane (30ml) and ozonolysed at -70°C until a green/blue colour was obtained. Argon was then passed through the solution. Triphenylphosphine (194mg, 0.74mmol) was added and the mixture warmed to room temperature. Evaporation to low volume followed by chromatography on silica eluting with

dichloromethane/methanol mixtures gave the title compound (106mg); ν_{max} (KBr) 3436, 1684, 1603cm^{-1}; λ_{max} (EtOH) 256nm (E_m 8,550), 324.5 (11,750); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 2.65 (3H, s, COMe), 6.31 (1H, s, 2-H), 7.96 and 8.02 (4H, ABq, J 8.5Hz); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 26.8 (COMe), 31.6 (C-9), 39.7 (C-8), 42.8 (C-12), 43.0 (C-4), 55.6 (C-10), 61.2 (C-11), 65.5 (C-16), 69.0 (C-6), 70.3 (C-13), 71.3 (C-7), 73.9 (C-5), 98.3 (C-2), 127.2 (C-3'5'), 128.6 (C-2',6'), 138.3 (C-1'), 139.6 (C-4'), 179.8 (C-3), 197.5 (C-1), 197.6 (COMe); (Found: M^+ 448.2106. $C_{24}H_{32}O_8$ requires M 448.2097). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

Example 5

3R,4R-Dihydroxy-2S-[4-(4-dimethylaminophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-dimethylamino-phenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

A solution of diisopropylamine (0.48ml, 3.36mmol) in dry THF (25ml) under argon at -30°C was treated dropwise with a solution of n-butyllithium (1.5M, 2.24ml, 3.36mmol) in hexane. After 15min the mixture was cooled to -70°C and treated dropwise over 5min with a solution of tristrimethylsilylmonone (1.45g, 2.8mmol) in THf (7ml). After 1 hour the mixture was treated with a solution of p-dimethylaminobenzaldehyde (447mg, 3.2mmol) in THF (2ml). After a further hour saturated ammonium chloride was added. The mixture was extracted with ethyl acetate and the organic phase washed with brine, then dried and evaported. Chromatography on silica eluting with ethyl acetate/hexane mixtures gave the title compound (300mg); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 2.94 (6H, s, NMe_2), 4.06-4.19 (1H, m, 5-H), 5.05-5.14 (1H, m, 1-H), 6.65-6.86 (2H, m, 2',6'-H_2), 7.25 (2H, d, J 6.5Hz, 3'5'-H_2).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-dimethylamino-

phenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

A solution of the product from 5a (300mg, 0.45mmol) in dioxan (15ml) was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (102mg, 0.45mmol). After 5min the mixture was diluted with dichloromethane, filtered through Kieselguhr, washing with dichloromethane, and the filtrate evaporated. Chromatography on silica eluting with ethyl acetate/hexane mixtures gave the title compound (250mg, 83%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.06 (6H, s, -NMe_2), 6.17 (1H, s, 2-H), 6.68 (2H, d, J 9.0Hz, 3'5'-H_2), 7.82 (2H, d, J 9.0Hz, 2',6'-H_2). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[4-(4-dimethylaminophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

A solution of the product of 5b (100mg, 0.15mmol) in THF (5ml) was treated with 0.4M HCl (1ml). After 2min saturated sodium hydrogen carbonate solution (1ml) was added. The mixture was then extracted with ethyl acetate and the organic phase washed with brine, dried and evaporated. Chromatography on silica eluting dichloromethane/methanol mixtures gave the title compound (64mg, 95%); ν_{max} (KBr) 3424, 1715, 1597, 1524cm^{-1}; λ_{max} (EtOH) 370nm (E_m 29,750); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.07 (6H, s, -NMe_2), 6.16 (1H, s, 2-H), 6.64 (2H, d, J 9.0Hz, 3',5'-H_2), 7.82 (2H, d, J 9.0Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 31.7 (C-9), 39.6 (C-8), 39.7 (NMe_2), 42.5 (C-4), 42.6 (C-12), 55.6 (C-10), 61.3 (C-11), 65.6 (C-16), 69.3 (C-6), 70.3 (C-13), 71.3 (C-7), 74.0 (C-5), 95.6 (C-2), 111.1 (C-3',5'), 121.1 (C-1'), 129.3 (C-2',6), 153.4 (C-4'), 183.8 (C-3), 192.1 (C-1); (Found: M^+, 449.2423. $C_{24}H_{35}NO_7$ requires M 449.2414).

Example 6

3R,4R-Dihydroxy-2S-(2,4-dioxo-4-(furan-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(furan-3-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a and on the same scale, furan-3-carboxaldehyde (0.28ml, 3.2mmol) was reacted to give the title compound (1.3g, 75%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.07-4.18 (1H, m, 5-H), 5.05-5.18 (1H, m, 1-H), 6.38-6.42 (1H, m, 4'-H), 7.35-7.44 (2H, m, 2',5'-H_2).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(furan-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

The product from 6a (650mg) in benzene (30ml) was treated with manganese dioxide (1.76g) and refluxed with provision for azeotropic removal of water (Dean and Stark apparatus containing molecular sieves 4A) for 4 hours. The mixture was diluted with dioxan filtered through Kieselguhr, washing pad well with dioxan and evaporated. Chromatography on silica eluting ethyl acetate/hexane mixtures gave the title compound (267mg, 41%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 5.92 (1H, s, 2-H), k6.70 (1H, d, J 1.2Hz, 4'-H), l7.45 (1H, m, 5'-H), and 7.99 (1H, s, 2'-H). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 6b (200mg, 0.33mmol) was deprotected to give the title compound (120mg, 93%); ν_{max} (KBr) 3427, 1718, 1620, 1509cm^{-1}; λ_{max} (EtOH) 303.5nm (E_m 11,075); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 5.93 (1H, s, 2-H), 6.69 (1H, d, J 1.6Hz, 4'-H), 7.46 (1H, s, with further fine coupling, 5'-H), 8.02 (1H, bs, 2'-H); δ_C ($CDCl_3$) 12.5 (C-17), 20.6 (C-14), 31.4 (C-9), 39.4 (C-8), 41.9 (C-4), 42.6 (C-12), 55.5 (C-10), 61.1 (C-11), 65.4 (C-16), 68.5 (C-6), 70.1 (C-13), 71.1 (C-7), 73.6 (C-5), 98.1 (C-2), 107.8 (C-2'), 123.8 (C-3'), 144.1 (C-4'), 145.6 (C-3'), 178.3 (C-3), 188.1

(C-1); M/Z 396 (M^+, 100%) and 95 (100). (Found M^+ 396.1788; $C_{20}H_{28}O_8$ requires M 396.1784). The ^1H nmr spectrum indicated that the material was essentially in enolic form.

Example 7

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(1-methylpyrazol-4-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, 1-methylpyrazole-4-carboxaldehyde (352mg, 3.2mmol) was reacted to give the title compound (1.25g, 71%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.87 (3H, s, 1'-Me), 4.07-4.17 (1H, m, 5-H), 5.12-5.22 (1H, m 1-H), 7.36 (1H, s, 5'-H), 7.43 (1H, s, 3'-H).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)-but-1-yl]5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 7a (450mg, 0.7mmol) in benzene (15ml) was reacted with manganese dioxide (1.25g) for 1 1/2 hours to give the title compound (260mg, 58%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 3.94 (3H, s, NMe), 5.92 (1H, s, 2-H), 7.86 (2H, bs, 3',5'-H_2). The ^1H nmr spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 7b (250mg, 0.4mmol) was deprotected to give the title compound (125mg, 76%); ν_{max} (KBr) 3424, 1718, 1617, 1546cm^{-1}; λ_{max} (EtOH) 308nm (ε_m 10,030); δ_H

($CDCl_3$) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 3.94 (3H, s, NMe), 5.94 (1H, s, 2-H), 7.87 (2H, s, 3',5'-H_2); δ_C ($CDCl_3$); 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 39.3 (C-8), 39.6 (1'-Me), 41.5 (C-4), 42.8 (C-12), 55.6 (C-10), 61.1 (C-11), 65.5 (C-16), 68.9 (C-6), 70.3 (C-13), 71.2 (C-7), 73.9 (C-5), 97.6 (C-2), 120.3 (C-4'), 131.7 (C-3'), 139.3 (C-5'), 179.6 (C-3), 191.5 (C-1); MZ (FAB) MNa± 433, MH± 411. The ^1H spectrum indicated that the title compound was essentially in the enolic form. Extra signals were observed in the ^{13}C nmr spectrum which were identified as being from the presence of a small amount of the diketone form.

Example 8

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(furan-2-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, furan-2-carboxaldehyde (0.28ml, 3.36mmol) was reacted to give the title compound (1.196g, 69%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 4.10-4.22 (1H, m, 5-H), 5.15-5.22 (1H, m, 1-H), 6.27 (1H, m, 3'-H), 6.33-6.35 (1H, m, 4'-H), and 7.37 (1H, m, 5'-H); m/z 614 (M^+, 1%) and 117 (100). (Found: M^+, 614.3136. $C_{29}H_{54}O_8Si_3$ requires M, 614.3127).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 8a (1.176g, 1.9mmol) in benzene (40ml) was reacted with manganese dioxide (4.3g) for 1 1/2 hours to give the title compound (0.601g, 51%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 6.17 (1H, s, 2-H), 6.54 (1H, dd, 3.6 and 1.7Hz, 4'-H), 7.15 (1H, d, 3.7Hz, 3'-H), and 7.57 (1H, m, 5'-H); m/z 612 (M^+, 1%), 597 (1), 117 (90), and 73 (100). (Found: M^+,

612.2979. $C_{29}H_{52}O_8Si_3$ requires M, 612.2970). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 8b (0.6g, 0.98mmol) was deprotected to give the title compound (0.289g, 74%); ν_{max} (KBr) 3472, 1627, 1467, 1087, and 1046cm^{-1}; λ_{max} (EtOH) 321.5nm (ε_m 20,440); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 6.17 (1H, s, 2-H), 6.55 (1H, dd, J 3.5 and 1.7Hz, 4'-H), 7.16 (1H, d, J 3.5Hz, 3'-H), and 7.58 (1H, s, with fine coupling, 5'-H); δ_C ($CDCl_3/CD_3OD$); 12.5 (C-17), 20.6 (C-14), 31.6 (C-9), 39.6 (C-8), 41.2 (C-4), 42.6 (C-12), 55.6 (C-10), 61.1 (C-11), 65.6 (C-16), 68.7 (C-6), 70.1 (C-7), 71.0 (C-13), 74.0 (C-5), 96.8 (C-2), 112.5 (C-4'), 116.0 (C-3'), 146.2 (C-5'), 150.1 (C-2'), 175.1 (C-3), and 191.1 (C-1); m/z 396 (M^+, 1%) and 137 (100). (Found: M^+, 396.1784. $C_{20}H_{28}O_8$ requires M, 396.1784). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 9

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(pyrid-4-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, pyridine-4-carboxaldehyde (0.32ml, 3.36mmol) was reacted to give the title compound (1.20g, 68%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.14-5.22 (1H, m, 1-H), 7.34-7.38 (2H, m, 3' and 5'-H), and 8.56-8.60 (2H, m, 2' and 6'-H); m/z 625 (M^+, 3%) and 117 (100). (Found: M^+, 625.3288. $C_{30}H_{55}NO_7Si_3$ requires M, 625.3286).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 9a(1.18g, 1.88mmol) in benzene (60ml) was reacted with manganese dioxide (3.3g) for 2 hours to give the title compound (0.556g, 47%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 6.33 (1H, s, 2-H), 7.75-7.79 (2H, m, 3' and 5'-H), and 8.76 (2H, br, 2' and 6'-H); m/z 623 (M^+, 4%), 117 (99), and 73 (100). (Found: M^+, 623.3131. $C_{30}H_{53}NO_7Si_3$ requires M, 623.3130). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 9b (0.535g, 0.86mmol) was deprotected to give the title compound (0.321g, 92%); ν_{max} (KBr) 3421, 1595, 1550, 1455, 1111, and 1062cm^{-1}; λ_{max} (EtOH) 316.5nm (ε_m 10,786); δ_H ($CDCl_3/CD_3OD$) inter alia 0.93 (3H, d, J 7.1Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 2.63 (1H, dd, J 15.1 and 8.5Hz, 4-H), 2.73 (1H, dd, J 7.6 and 2.1Hz, 11-H), 2.82 (1H, td, J 5.7 and 2.1Hz, 10-H), 2.98 (1H, dd, J 15.1 and 3.3Hz, 4-H), 6.33 (1H, s, 2-H), 7.69-7.73 (2H, m, 3' and 5'-H), and 8.70-8.75 (2H, m, 2' and 6'-H); δ_C ($CDCl_3/CD_3OD$); 12.5 (C-17), 20.6 (C-14), 31.6 (C-9), 39.8 (C-8), 42.6 (C-12), 43.2 (C-4), 55.6 (C-10), 61.0 (C-11), 65.6 (C-16), 68.5(C-6), 70.1 (C-7), 70.9 (C-13), 73.9 (C-5), 98.6 (C-2), 120.6 (C-3' and 5'), 141.9 (C-4'), 150.2 (C-2' and 6'), 177.1 (C-3), and 198.6 (C-1); m/z 407 (M^+, 6%) and 148 (100). (Found: M^+, 407.1954. $C_{21}H_{29}NO_7$ requires M, 407.1944). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 10

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(pyrid-3-yl)-

4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.34g, 2.58mmol) and pyridine-3-carboxaldehyde (0.29ml, 3.1mmol) were reacted to give the title compound (1.154g, 71%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.19-5.27 (1H, m, 1-H), 7.33 (1H, dd, J 7.8 and 4.9Hz 5'-H), 7.77-7.82 (1H, m, 4'-H), 8.54 (1H, dd, J 4.7 and 1.1Hz, 6'-H), and 8.62 (1H, d, J 1.6Hz, 2'-H) (contains approximately 4% pyridine-3-carboxaldehyde).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 10a(1.10g, 1.76mmol) in benzene (70ml) was reacted with manganese dioxide (4.0g) for 2 1/2 hours to give the title compound (0.513g, 47%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 6.29 (1H, s, 2-H), 7.43 (1H, dd, J 7.9 and 4.9Hz, 5'-H), 8.20 (1H, dt, J 7.9 and 1.7Hz, 4'-H), 8.73 (1H, m, 6'-H), and 9.09 (1H, s with fine coupling, 2'-H); m/z 623 (M^+, 75%), and 331 (100). (Found: M^+, 623.3118. $C_{30}H_{53}NO_7Si_3$ requires M, 623.3130). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 10b (0.50g, 0.80mmol) was deprotected to give the title compound (0.262g, 81%); ν_{max} (KBr) 3411, 1597, 1452, 1111, and 1043cm^{-1}; λ_{max} (EtOH) 312nm (ε_m 12,785); δ_H ($CDCl_3$) 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.4Hz, 14-H_3), 6.34 (1H, s, 2-H), 7.42 (1H, dd, J 8.0 and 4.9Hz, 5'-H), 8.18 (1H, dt, J 8.0 and 1.7Hz, 4'-H), 8.72 (1H, dd, J 4.9 and 1.4Hz, 6'-H), and 9.07 (1H, d, J 1.8Hz, 2'-H); δ_C ($CDCl_3$) 12.8 (C-17), 20.8 (C-14), 31.6 (C-9), 39.8 (C-8), 42.5 (C-4), 42.8 (C-12), 55.5 (C-10), 61.0 (C-11), 65.5 (C-16), 68.6 (C-6), 70.3 (C-7), 71.2 (C-13), 73.6 (C-5), 97.9 (C-2), 123.6 (C-5'), 130.4 (C-3'),

134.7 (C-4'), 148.1 (C-6'), 152.4 (C-2'), 179.4 (C-3), and 196.4 (C-1); m/z 407 (M^+, 17%)
and 106 (100). (Found: M^+, 407.1946. $C_{21}H_{29}NO_7$ requires M, 407.1944). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 11

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-2-yl)but-1-yl]but-1-yl]5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(pyrid-2-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and pyridine-2-carboxaldehyde (0.23ml, 2.4mmol) were reacted to give the title compound (0.804g, 64%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.21-5.27 (1H, m, 1-H), 7.22 (1H, m, 5'-H), 7.51 (1H, d, J 7.8Hz, 3'-H), 7.73 (1H, t with further fine coupling, J 7.7Hz, 4'-H), and 8.54 (1H, d, J 4.7Hz, 6'-H); m/z 625 (M^+, 3%), 129 (100), 117 (100), and 73 (100). (Found: M^+, 625.3281. $C_{30}H_{55}NO_7Si_3$ requires M, 625.3286).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(pyrid-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 11a(0.790g, 1.26mmol) in benzene (35ml) was reacted with manganese dioxide (2.5g) for 2 hours to give the title compound (0.275g, 35%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 6.89 (1H, s, 2-H), 7.37-7.44 (1H, m, 5'-H), 7.83 (1H, dt, J 1.7 and 7.8Hz, 4'-H), 8.08 (1H, d, J 7.8Hz, 3'-H), 8.67 (1H, d, J 4.2Hz, 6'-H); m/z 623 (M^+, 14%), 148 (75), 117 (82), and 73 (100). (Found: M^+, 623.3143. $C_{30}H_{53}NO_7Si_3$ requires M, 623.3130). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 11b (0.260g, 0.42mmol) was deprotected to give the title compound (0.042g, 25%); ν_{max} (KBr) 3399, 1607, 1587, 1516, 1449, and 1045cm^{-1}; λ_{max} (EtOH) 314nm (ε_m 11,010); δ_H [$(CD_3)_2CO$] inter alia 0.92 (3H, d, J 7.0Hz, 17-H_3), 1.16 (3H, d, J 6.4Hz, 14-H_3), 6.98 (1H, s, 2-H), 7.57 (1H, ddd, J 7.4, 4.8, and 1.4Hz, 5'-H), 8.00 (1H, dt, J 7.7 and 1.7Hz, 4'-H), 8.10 (1H, d, J 7.8Hz, 3'-H), and 8.71 (1H, d, with further fine coupling, J 4.8Hz, 6'-H); m/z (TSP) 408 (MH^+, 65%) and 99 (100); m/z 407 (M^+, 40%) and 122 (100). (Found: M^+, 407.1950. $C_{21}H_{29}NO_7$ requires M, 407.1944).

Example 12

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl) but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3-methyl-isoxazol-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 3-methylisoxazole-5-carboxaldehyde (0.267g, 2.4mmol) were reacted to give the title compound (0.834g, 66%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 2.29 (3H, s, 3'-CH_3), 5.18-5.27 (1H, m, 1-H), and 6.10 (1H, s, 4'-H); m/z 629 (M^+, 8%), 129 (100), 117 (100), and 73 (100). (Found: M^+, 629.3260. $C_{29}H_{55}NO_8Si_3$ requires M, 629.3236).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 12a(0.815g,

1.29mmol) in benzene (35ml) was reacted with manganese dioxide (2.04g) for 2 hours to give the title compound (0.360g, 42%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 2.37 (3H, s, 3'-CH_3), 6.32 (1H, s, 2-H), and 6.69 (1H, s, 4'-H); m/z (TSP) 645 (MNH_4^+, 100%) and 628 (MH^+, 65); m/z 627 (M$^+$, 10%), 612 (12), 117 (100), and 73 (100). (Found: M$^+$, 627.3104. $C_{29}H_{53}NO_8Si_3$ requires M, 627.3079). The ^{1}H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 12b (0.380g, 0.6mmol) was deprotected to give the title compound (0.167g, 68%); ν_{max} (KBr) 3395, 1617, 1584, 1512, 1457, 1412, and 1055cm^{-1}; λ_{max} (EtOH) 330nm (ε_m 13,500); δ_H [$(CD_3)_2SO$] inter alia 0.83 (3H, d, J 7.1Hz, 17-H_3), 1.07 (3H, d, J 6.4Hz, 14-H_3), 2.25 (3H, s, 3'-CH_3), 5.83 (1H, s, 2-H), and 6.64 (1H, s, 4'-H); δ_C (CD_3OD) 11.3 (isox-CH_3), 12.3 (C-17), 20.4 (C-14), 32.9 (C-9), 41.5 (C-8), 43.7 (C-12), 45.1 (br, C-4), 56.9 (C-10), 61.3 (C-11), 66.5 (C-16), 70.1 (C-6), 70.8 (C-13), 71.6 (C-7), 76.0 (br, C-5), 99.0 (br, C-2), 106.6 (br, C-4'), 161.9 (C-3'), 170.5 (br, C-5'), 171.4 (br, C-3), and 197.0 (br, C-1); m/z (FAB, thioglycerol) 450 (MK^+) and 434 (MNa^+); m/z 411 (M$^+$, 0.1%), 125 (80), and 43 (100). (Found: M$^+$, 411.1892. $C_{20}H_{29}NO_8$ requires M, 411.1893). The ^{1}H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 13

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3-methoxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale,

3-methoxybenzaldehyde (0.39ml, 3.2mmol) was reacted to give the title compound (1.06g, 56%);
δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.82 (3H, s, OMe), 4.07-4.20 (1H, m, 5-H), 5.09-5.21 (1H, m, 1-H), 6.78-6.85 (1H, m, 6'-H), 6.90-6.99 (2H, m, 2', 4'-H_2), 7.23-7.32 (1H, m, 5'-H); m/z 654 (M^+, 0.5%) and 117 (100). (Found: M^+, 654.3456. $C_{32}H_{58}O_8Si_3$ requires M, 654.3440).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 13a(1.0g, 1.49mmol) in benzene (50ml) was reacted with manganese dioxide (3.0g) for 3 hours to give the title compound (0.610g, 61%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 3.86(3H, s, OMe), 6.25 (1H, s, 2-H), 7.06 (1H, dd, J 1.6, 8.0Hz, 6'-H), 7.35 (1H, dd, J 7.8, 8.0Hz, 5'-H), 7.40-7.51 (2H, m, 2', 4'-H_2); m/z 652 (M^+, 1%) and 41 (100). (Found: M^+, 652.3280. $C_{35}H_{56}O_8Si_3$ requires M, 652.3280).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methoxyphenyl but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 13b (250mg, 0.37mmol) was deprotected to give the title compound (140mg, 87%); ν_{max} (KBr) 3430, 1718, 1576, 1457cm^{-1}; λ_{max} (EtOH) 309nm (ε_m 15,360); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.4Hz, 14-H_3), 3.86 (3H, s, OMe), 6.26 (1H, s, 2-H), 7.08 (1H, d with further fine coupling, J ca.8.0Hz, 6'-H), 7.30-7.52 (3H, m, 2', 4', 5'-H_3); δ_C (d_4-MeOH), 12.0 (C-17), 20.0 (C-14), 32.6 (C-9), 41.3 (C-8), 42.6 (C-4), 43.4 (C-12), 55.6 (C-10), 56.5 (OMe), 60.9 (C-11), 66.1 (C-16), 69.5 (C-6), 70.4 (C-13), 71.2 (C-7), 75.1 (C-5), 98.1 (C-2), 113.8 (C-5'), 119.0 (C-4'), 120.1 (C-6'), 130.5 (C-3), 137.1(C-1'), 161.0 (C-3'), 183.1 (C-3), 196.3 (C-1); m/z 436 (M^+, 0.2%) and 135 (100). (Found: M^+, 436.2105. $C_{27}H_{32}O_8$ requires M, 436.2097). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 14

3R,4R-Dihydroxy-2S-[4-(4-cyanophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-cyanophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, 4-cyanobenzaldehyde (419mg, 3.2mmol) was reacted to give the title compound (1.25g, 68%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.08-4.19 (1H, m, 5-H), 5.16-5.28 (1H, m, 1-H), 7.49 (2H, d, J 8.2Hz, 2', 6'-H_2), 7.62 (2H, d, J 8.2Hz, 3', 5'-H_2).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-cyanophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 14a(1.25g) in benzene (65ml) was reacted with manganese dioxide (3.5g) for 1 hour to give the title compound (625mg, 50%); δ_H ($CDCl_3$) 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 1.31-1.45 (1H, m, 8-H), 1.50-1.66 (2H, m, 9-H), 1.80-1.90 (1H, m, 12-H), 2.39 (1H, dd, J 10.2, 14.8Hz, 4-H), 2.62-2.75 (2H, m, 10, 11-H_2), 2.86 (1H, dd, J 2.6, 14.7Hz, 4-H), 3.46 (1H, dd, J 2.4, 9.2Hz, 6-H), 3.57 (1H, d, J 11.3Hz, 16-H), 3.77-3.92 (2H, m, 7, 13-H_2), 3.96 (1H, d, J 11.3Hz, 16-H), 4.07-4.20 (1H, m, 5-H), 6.28 (1H, s, 2-H), 7.74 (2H, d, J 8.5Hz, 3', 5'-H_2), 7.97 (2H, d, J 8.5Hz, 2', 6'-H_2). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[4-(4-cyanophenyl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 14b (200mg,

0.31mmol) was deprotected to give the title compound (95mg, 71%); ν_{max} (KBr) 3431, 2230, 1597, 1558cm^{-1}; λ_{max} (EtOH) 321.5nm (ε_m 16,280); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 6.29 (1H, s, 2-H), 7.75 (2H, d, J 8.4Hz, 3', 5'-H_2), 7.97 (2H, d, J 8.4Hz, 2', 6'-H_2); δ_C ($CDCl_3$) 13.1 (C-17), 21.2 (C-14), 31.9 (C-9), 40.1 (C-8), 43.2 (C-12), 43.3 (C-4), 56.0 (C-10), 61.6 (C-11), 66.0 (C-16), 69.2 (C-6), 70.6 (C-13), 71.7 (C-7), 74.2 (C-5), 98.8 (C-2), 115.8 (C-1'), 118.4 (C-4'), 127.8 (C-2', 6'), 132.8 (C-3', 5'), 138.7(CN),179.1 (C-3), 198.1 (C-1); m/z (FAB) 454 (MNa^+). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 15

3R,4R-Dihydroxy-2S-[4-(4-chlorophenyl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-chlorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, 4-chlorobenzaldehyde (450mg, 3.2mmol) was reacted to give the title compound (1.4g, 76%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.18 (3H, d, J 6.4Hz, 14-H_3), 4.07-4.18 (1H, m, 5-H), 5.08-5.20 (1H, m, 1-H), 7.28-7.32 (4H, m, Ar); m/z 658 (M^+, 0.01%) and 117 (100). (Found: M^+, 658.2947. $C_{31}H_{55}O_7ClSi_3$ requires M, 658.2944).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-chlorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 15a(700mg, 1.06mmol) in benzene (30ml) was reacted with manganese dioxide (1.75g) for 2 hours to give the title compound (296mg, 42%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.10 (3H, d, J 6.3Hz, 14-H_3), 3.94-4.08 (1H, m, 5-H), 6.23 (1H, s, 2-H), 7.41 (2H, d, J 8.6Hz, 3', 5'-H_2), 7.82 (2H, d, J 8.6Hz, 2', 6'-H_2); m/z, 656 (M^+, 5%) and 117 (100). (Found: M^+, 656.2803.

$C_{31}H_{53}O_7ClSi_3$ requires M, 656.2788).

c) 3R,4R-Dihydroxy-2S-[4-(4-chlorophenyl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 15b (296mg, 0.45mmol) was deprotected to give the title compound (160mg, 80%); ν_{max} (KBr) 3424, 1718, 1595, 1486, 1451, 1380cm^{-1}; λ_{max} (EtOH) 313nm (ε_m 17,760) and 255 (7,460); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 6.20 (1H, s, 2-H), 7.43 (2H, d, J 8.6Hz, 3', 5'-H_2), 7.82 (2H, d, J 8.6Hz, 2', 6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.7 (C-4), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 69.0 (C-6), 70.3 (C-13), 71.3 (C-7), 73.9 (C-5), 97.4 (C-2), 128.4 (C-3', C-5'), 129.0 (C-2', C-6'), 134.6 (C-1'), 140.4 (C-4'), 181.1 (C-3), 196.0 (C-1); m/z 441 (MH^+, 2%) and 139 (100). (Found: M^+, 441.1680. $C_{22}H_{30}O_7Cl$ requires M, 441.1680). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 16

3R,4R-Dihydroxy-2S-[4-(4-diethoxymethylphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-diethoxy-methylphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, terephthalaldehyde-mono, diethyl acetal (666mg, 3.2mmol) was reacted to give the title compound (1.52g, 75%); δ_H (d_4-MeOH) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.02-4.16 (1H, m, 5-H), 5.10-5.19 (1H, m, 1-H), 5.47 (1H, s, ArCH-$(OEt)_2$), 7.36 and 7.42 (4H, ABq, J 8.4Hz); m/z (FAB) 749 (MNa^+).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-diethoxy methylphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-

trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 16a(1.0g, 1.38mmol) in benzene (50ml) was reacted with manganese dioxide (2.5g) for 2 hours to give the title compound (535mg, 53%); δ_H (d_4-MeOH) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 1.22 (6H, t, J 7.1Hz, -$(OEt)_2$), 4.07-4.17 (1H, m, 5-H), 5.55 (1H, s, Ar-CH-$(OEt)_2$), 6.41 (1H, s, 2-H), 7.56 (2H, d, J 8.3Hz, 3', 5'-H_2), 7.92 (2H, d, J 8.3Hz, 2', 6'-H_2); m/z 724 (M^+, 0.1%) and 432 (100). (Found: M^+, 724.3860. $C_{36}H_{64}O_9Si_3$ requires M, 724.3858). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[4-(4-diethoxymethylphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 1d, the product from 16b (150mg, 0.21mmol) in ethanol (5ml) was deprotected to give the title compound (60mg, 57%); λ_{max} (EtOH) 315nm (ε_m 18,870) and 252 (7,350); δ_H (d_6-acetone) inter alia 0.92 (3H, d, J 7.0Hz, 17-H_3), 1.10-1.30 (9H, m, 17-H_3, 2 x OEt), 5.58 (1H, s, -CH-$(OEt)_2$), 6.52 (1H, s, 2-H), 7.59 (2H, d, J 8.4Hz, 3', 5'-H_2), 7.99 (2H, d, J 8.4Hz, 2', 6'-H_2); δ_C (d_6-acetone) 12.3 (C-17), 15.5 (-CH_2Me), 20.8 (C-14), 32.7 (C-9), 41.3 (C-8), 43.0 (C-4), 43.3 (C-12), 55.8 (C-10), 60.4 (C-11), 61.6 (-CH_2Me), 66.0 (C-16), 69.4 (C-6), 70.1 (C-7), 71.1 (C-13), 75.1 (C-5), 98.0 (C-2), 101.6 (CH-$(OEt)_2$), 127.6 and 127.7 (C-2', 6', 3', 5'), 135.5 (C-4'), 144.9 (C-1'), 183.0 (C-1), 197.2 (C-3). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 17

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-formylphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-formylphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsOyyloxy-4S-methylhexyl)tetrahydropyran

The product from 16b (110mg) was dissolved in acidic chloroform (10ml) [standard solution: chloroform (100ml):concentrated hydrochloric acid (1 drop)]. After 1 1/2 hours the mixture was evaporated and chromatographed on silica eluting with ethyl acetate/ hexane mixtures to give the title compound (60mg, 60%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.2Hz, 14-H_3), 4.08-4.22 (1H, m, 5-H), 6.33 (1H, s, 2-H), 7.95 and 8.04 (4H, ABq, J 8.4Hz, Ar), 10.09 (1H, s, -CHO); m/z (FAB) 673 (MNa^+).

b) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-formylphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 17a (50mg, 0.08mmol) was deprotected to give the title compound (33mg, 100%); ν_{max} (KBr) 3427, 1701, 1602, 1564cm^{-1}; λ_{max} (EtOH) 322.5nm (ε_m 16,240) and 258 (9,430); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 6.33 (1H, s, 2-H), 7.94 and 8.01 (4H, ABq, J 8.3Hz, Ar), 10.06 (1H, s, -CHO); δ_C ($CDCl_3$) 12.8 (C-17), 20.9 (C-14), 31.6 (C-9), 39.8 (C-8), 42.9 (C-12), 43.2 (C-4), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 69.0 (C-6), 70.3 (C-7), 71.4 (C-13), 73.9 (C-5), 98.2 (C-2), 127.6 (C-3', 5'), 129.8 (C-2', 6'), 138.6 (C-4'), 139.5 (C-1'), 179.3 (C-1), 191.6 (CHO), 197.9 (C-3); m/z 434 (M^+, 2%) and 133 (100); (Found: M^+, 434.1944. $C_{23}H_{30}O_8$ requires M, 434.1941). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 18

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(4-nitrophenyl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, 4-nitrobenzaldehyde (483mg, 3.2mmol) was reacted to give the title

compound (1.42g, 76%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 4.08-4.17 (1H, m, 5-H), 5.22-5.33 (1H, m, 1-H), 7.55 (2H, dd, J 1.5, 8.7Hz, 2', 6'-H_2), 8.21 (2H, d, J 8.7Hz, 3', 5'-H_2); m/z 669 (M^+, 5%) and 117 (100). (Found: M^+, 669.3198. $C_{31}H_{55}NO_9Si_3$ requires M, 669.3185).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-nitrophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 18a(1.0g, 1.49mmol) in benzene (50ml) was reacted with manganese dioxide (2.5g) for 45 minutes to give the title compound (618mg, 68%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.08-4.22 (1H, m, 5-H), 6.32 (1H, s, 2-H), 8.04 (2H, d, J 8.8Hz, 2', 6'-H_2), 8.30 (2H, d, J 8.8Hz, 3', 5'-H_2); m/z 667 (M^+, 5%) and 117 (100). (Found: M^+, 667.3043. $C_{31}H_{53}NO_9Si_3$ requires M, 667.3043). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 18b (200mg, 0.3mmol) was deprotected to give the title compound (83mg, 61%); ν_{max} (KBr) 3112, 1588, 1488, 1451, 1346cm^{-1}; λ_{max} (EtOH) 331.5nm (ε_m 13,490) and 253.5 (9,430); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.2Hz, 14-H_3), 6.32 (1H, s, 2-H), 8.03 (2H, d, J 8.9Hz, 2', 6'-H_2), 8.30 (2H, d, J 8.9Hz, 3', 5'-H_2); δ_C ($CDCl_3$) 12.8 (C-17), 20.9 (C-14), 31.6 (C-9), 39.8 (C-8), 42.9 (C-12), 43.1 (C-4), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 68.9 (C-7), 70.4 (C-6), 71.4 (C-13), 73.9 (C-5), 98.8 (C-2), 123.8 (C-2', 6'), 128.0 (C-3', 5'), 140.0 (C-1'), 149.9 (C-4'), 178.2 (C-1), 198.1 (C-3); m/z (FAB) 469 (MNH_4^+) and 452 (MH^+). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 19

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-

(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(thien-2-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyl-oxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.15g, 2.22mmol) and thiophene-2-carboxaldehyde (0.24ml, 2.6mmol) were reacted to give the title compound (1.086g, 78%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 5.36-5.46 (1H, m, 1-H), 6.94-7.00 (2H, m, 3' and 4'-H), and 7.22-7.28 (1H, m, 5'-H); m/z 630 (M^+, 4%) and 117 (100). (Found: M^+, 630.2909. $C_{29}H_{54}O_7SSi_3$ requires M, 630.2898).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 19a (1.05g, 1.66mmol) in benzene (40ml) was reacted with manganese dioxide (2.6g) for 1 3/4h to give the title compound (0.684g, 66%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 6.13 (1H, s, 2-H), 7.12 (1H, dd, J 3.9 and 4.9Hz, 4'-H), 7.59 (1H, dd, J 0.9 and 4.9Hz, 3'-H), and 7.70 (1H, dd, J 0.9 and 3.9Hz, 5'-H); m/z 628 (M^+, 2%), 336 (90), 117 (100), and 73 (99). (Found: M^+, 628.2759. $C_{29}H_{52}O_7SSi_3$ requires M, 628.2742). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 19b (0.670g, 1.06mmol) was deprotected to give the title compound (0.367g, 84%); υ_{max} (KBr) 3421, 1611, 1412, 1272, 1110, and 1043cm^{-1}; λ_{max} (EtOH) 325nm (ε_m 15,308); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 6.13 (1H, s, 2-H), 7.14 (1H, dd, J 3.9 and 4.9Hz, 4'-H), 7.62 (1H, dd, J 4.9 and 0.9Hz, 3'-H), and 7.72 (1H, dd, J 3.9 and 0.9Hz, 5'-H); δ_C ($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 39.6 (C-8), 40.8 (C-4),

42.8 (C-12), 55.6 (C-10), 61.2 (C-11), 65.6 (C-16), 68.8 (C-6), 70.3 (C-7), 71.3 (C-13), 74.0 (C-5), 97.3 (C-2), 128.3, 130.6 and 132.6 (C-3', 4', 5'), 140.9 (C-2'), 180.7 (C-3), and 189.3 (C-1); m/z 412 (M^+, 1%) and 111 (100). (Found: M^+, 412.1559. $C_{20}H_{28}O_7S$ requires M, 412.1556). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 20

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(thien-3-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.15g, 2.22mmol) and thiophene-3-carboxaldehyde (0.23ml, 2.6mmol) were reacted to give the title compound (0.953g, 68%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.21-5.29 (1H, m, 1-H), 7.04-7.09 (1H, m, 4'-H), 7.22-7.24 (1H, m, 2'-H), and 7.28-7.32 (1H, m, 5'-H); m/z 630 (M^+, 0.1%), 226 (65), 129 (92), 117 (88), and 73 (100). (Found: M^+, 630.2897. $C_{29}H_{54}O_7SSi_3$ requires M, 630.2898).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(thien-3-yl)but-1-yl)-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 20a (0.93g, 1.47mmol) in benzene (40ml) was reacted with manganese dioxide (2.5g) for 1 3/4h to give the title compound (0.537g, 58%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 6.10 (1H, s, 2-H), 7.34 (1H, dd, J 3.0 and 5.1Hz, 4'-H), 7.46 (1H, dd, J 1.1 and 5.1Hz, 5'-H), and 8.01 (1H, dd, J 1.1 and 3.0Hz, 2'-H); m/z 628 (M^+, 2%), 336 (78), 117 (85), and 73 (100). (Found: M^+, 628.2753. $C_{29}H_{52}O_7SSi_3$ requires M, 628.2742). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6c, the product from 20b (0.53g, 0.84mmol) was deprotected to give the title compound (0.309g, 89%); υ_{max} (KBr) 3417, 1609, 1508, 1258, 1109, and 1054cm^{-1}; λ_{max} (EtOH) 313nm (ε_m 16,375); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.2Hz, 14-H_3), 7.36 (1H, dd, J 2.9 and 5.1Hz, 4'-H), 7.45 (1H, dd, J 1.2 and 5.1Hz, 5'-H), and 8.04 (1H, dd, J 1.2 and 2.9Hz, 2'-H); δ_H ($CDCl_3$) 12.6 (C-17), 20.7 (C-14), 31.6 (C-9), 39.6 (C-8), 42.3 (C-4), 42.7 (C-12), 55.6 (C-10), 61.2 (C-11), 65.6 (C-16), 68.9 (C-6), 70.2 (C-7), 71.2 (C-13), 73.8 (C-5), 98.0 (C-2), 125.8, 126.6 and 129.9 (C-2', 4' and 5'), 138.1 (C-3'), 177.9 (C-3), and 194.9 (C-1); m/z 412 (M^+, 2%), 394 (7), 153 (70), and 111 (100). (Found: M^+, 412.1563. $C_{20}H_{28}O_7S$ requires M, 412.1556). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 21

3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)tetrahydropyran

a) 2-Dimethylaminopyridine-5-carboxaldehyde

5-Bromo-2-dimethylaminopyridine (1.005g, 5.0mmol) was dissolved in dry THF (25ml), cooled to -70°C, and treated dropwise with nbutyllithium (1.5M, 3.67ml, 5.5mmol). The mixture was stirred at -70°c for 1h, then N,N-dimethyl-formamide (1.16ml, 15mmol) added. Stirring was continued for a further hour, then the reaction quenched with saturated ammonium chloride. Water was added, and the mixture extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried and evaporated. The crude product was purified by column chromatography, on silica (36g), eluting with 20, 40 and 60% ethyl acetate in hexane, to give the title compound as white crystals (0.617g, 82%); m.p.55-55.5°C; δ_H ($CDCl_3$) 3.22 (6H, s, $N(CH_3)_2$), 6.56 (1H, d, J 9.0Hz, 3'-H), 7.92 (1H, dd, J 9.0 and 2.3Hz, 4'-H), 8.56 (1H, d, J 2.3Hz, 6'-H), and 9.77 (1H, s, CHO);

m/z 150 (M^+, 100%), 135 (83), 121 (88), and 44 (86). (Found: M^+, 150.0795. $C_8H_{10}N_2O$ requires M, 150.0793).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylamino-pyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-dimethylaminopyridine-5-carboxaldehyde (0.330g, 2.2mmol) were reacted to give the title compound (1.04g, 78%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.09 (6H, s, $N(CH_3)_2$), 5.04-5.11 (1H, m, 1-H), 6.52 (1H, d, J 8.8Hz, 3'-H), 7.52 (1H, dt, J 8.8 and 2.8Hz, 4'-H), and 8.13 (1H, d, J 2.3Hz, 6'-H); m/z 668 (M^+, 3%), 226 (100), 129 (90), 117 (80), and 73 (70). (Found: M^+, 668.3724. $C_{22}H_{60}N_2O_7Si_3$ requires M, 668.3708).

c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylamino-pyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 21b (1.01g, 1.51mmol) in benzene (35ml) was reacted with manganese dioxide (2.6g) for 3h to give the title compound (0.440g, 44%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.18 (6H, s, $N(CH_3)_2$), 6.13 (1H, s, 2-H), 6.51 (1H, d, J 9.1Hz, 3'-H), 7.96 (1H, dd, J 9.1 and 2.4Hz, 4'-H), and 8.72 (1H, d, J 2.4Hz, 6'-H); m/z 666 (M^+, 11%), 651 (3), and 149 (100). (Found: M^+, 666.3551. $C_{32}H_{58}N_2O_7Si_3$ requires M, 666.3552). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)tetrahydropyran

Using the method described in 5c, the product from 21c (0.420g, 0.63mmol) was deprotected to give the title compound (0.238g, 84%); υ_{max} (KBr) 3371, 1624, 1554, 1401, 1105, 1059, and 785cm^{-1}; λ_{max} (EtOH) 355nm (ε_m 35,913); δ_H ($CDCl_3/CD_3OD$) inter alia 0.93 (3H, d, J 7.0Hz,

17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 3.19 (6H, s, $N(CH_3)_2$), 6.13 (1H, s, 2-H), 6.53 (1H, d, J 9.1Hz, 3'-H), 7.94 (1H, dd, J 2.3 and 9.1Hz, 4'-H), and 8.71 (1H, d, J 2.3Hz, 6'-H); δ_C ($CDCl_3/CD_3OD$) 12.6 (C-17), 20.6 (C-14), 31.7 (C-9), 38.1 ($N(CH_3)_2$), 39.6 (C-8), 41.8 (C-4), 42.7 (C-12), 55.7 (C-10), 61.2 (C-11), 65.6 (C-16), 68.9 (C-6), 70.2 (C-7), 71.1 (C-13), 74.0 (C-5), 95.6 (C-2), 105.1 (C-4'), 118.0 (C-5'), 135.9 (C-3'), 149.1 (C-6'), 160.6 (C-2'), 183.3 (C-3), and 191.5 (C-1); m/z 450 (M^+, 5%) and 149 (100). (Found: M^+, 450.2372. $C_{23}H_{34}N_2O_7$ requires M, 450.2366). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 22

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-Methylthiopyridine-5-carboxaldehyde

Using the method described in 21a, 5-bromo-2-methylthio-pyridine (1.020g, 5mmol) was converted to the title compound (0.650g, 85%); m.p.43-45°C; δ_H ($CDCl_3$) 2.64 (3H, s, SCH_3), 7.31 (1H, d, J 8.5Hz, 3'-H), 7.94 (1H, dd, J 2.1 and 8.5Hz, 4'-H), 8.84 (1H, d, J 2.1Hz, 6'-H), and 10.00 (1H, s, CHO); m/z 153 (M^+, 100%), 152 (60), 124 (10), and 107 (48). (Found: M^+, 153.0247. C_7H_7NOS requires M, 153.0248).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-methylthiopyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (2.750g, 5.3mmol) and 2-methylthiopyridine-5-carboxaldehyde (0.890g, 5.8mmol) were reacted to give the title compound (2.840g, 80%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 2.59 (3H, s, SCH_3), 5.11-5.19 (1H, m, 1-H), 7.20 (1H, d, J 8.3Hz, 3'-H), 7.58 (1H, dt, J 8.3 and 2.8Hz, 4'-H), and 8.43 (1H, d, J 2.0Hz, 6'-H); m/z 671 (M^+, 2%), 129 (65), 117 (85), and 73 (100). (Found: M^+, 671.3187. $C_{31}H_{57}NO_7SSi_3$ requires M, 671.3164).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-

methylthiopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 22b (2.09g, 3.11mmol) in benzene (150ml) was reacted with manganese dioxide (2.8g) for 24h to give the title compound (1.340g, 64%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 2.61 (3H, s, SCH_3), 6.23 (1H, s, 2-H), 7.24 (1H, d, J 8.5Hz, 3'-H), 7.95 (1H, dd, J 2.2 and 8.5Hz, 4'-H), and 8.91 (1H, d, J 2.2Hz, 6'-H); m/z 669 (M^+, 3%), 152 (45), 117 (95), 75 (56), and 73 (100). (Found: M^+, 669.3018. $C_{31}H_{55}NO_7SSi_3$ requires M, 669.3007). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 22c (0.648g, 0.97mmol) was deprotected to give the title compound (0.341g, 78%); m.p.135.5-136°C; found C, 57.91; H, 6.88; N, 3.09; S, 7.10%. $C_{22}H_{31}NO_7S$ requires C, 58.26; H, 6.89; N, 3.09; S, 7.07%; υ_{max} (KBr) 3483, 3392, 1583, 1298, 1120, 1106, and 1061cm^{-1}; λ_{max} (EtOH) 336nm (ε_m 29,695); δ_H ($CDCl_3/CD_3OD$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.4Hz, 14-H_3), 2.61 (3H, s, SCH_3), 6.26 (1H, s, 2-H), 7.27 (1H, d, J 8.5Hz, 3'-H), 7.98 (1H, dd, J 8.5 and 2.3Hz, 4'-H), and 8.89 (1H, d, J 2.3Hz, 6'-H); δ_C ($CDCl_3/CD_3OD$) 12.3 (C-17), 13.2 (SCH_3), 20.3 (C-14), 31.6 (C-9), 39.7 (C-8), 42.0 (C-4), 42.5 (C-12), 55.6 (C-10), 60.9 (C-11), 65.6 (C-16), 68.4 (C-6), 70.0 (C-7), 70.6 (C-13), 73.9 (C-5), 97.0 (C-2), 120.8 (C-4'), 125.9 (C-5'), 133.9 (C-3'), 148.1 (C-6'), 165.2 (C-2'), 180.5 (C-3), and 194.6 (C-1); m/z 453 (M^+, 1%), 167 (100) and 152 (65). (Found: M^+, 453.1825. $C_{22}H_{31}NO_7S$ requires M, 453.1821). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 23

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphinylpyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

The product from 22c (0.215g, 0.32mmol) was dissolved in dichloromethane (9ml), cooled in an ice bath, saturated sodium hydrogen carbonate (0.5ml) and water (1.5ml) were then added, followed by 3-chloroperbenzoic acid (ca.95%, 0.064g, 0.35mmol). The mixture was stirred for 3/4h, then separated, and the aqueous extracted with dichloromethane (x2). The combined organic phases were washed with brine, dried and evaporated. The product was purified by column chromatography, on silica (10g), eluting with 30-40% ethyl acetate in hexane, to give the pure product (0.152g, 69%).

This material was dissolved in THF (7ml), water (0.7ml) added, followed by glacial acetic acid (0.7ml). Further portions of glacial acetic acid (5 x 0.4ml) were added over the following 28h. After this the solution was evaporated to dryness, and purified by column chromatography to give the title compound (0.064g, 62%); υ_{max} (KBr) 3405, 1602, 1451, 1109, 1084, and 1042cm^{-1}; λ_{max} (EtOH) 322nm (ε_m 15,550); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.23 (3H, d, J 6.3Hz, 14-H_3), 2.90 (3H, s, $SOCH_3$), 6.33 and 6.35 (1H, 2s, 2-H), 8.13 (1H, d, J 8.2Hz, 3'-H), 8.39 (1H, br d, 4'-H), and 9.06 (1H, s, 6'-H); δ_C ($CDCl_3$) 12.8 (C-17), 20.9 (C-14), 31.7 (C-9), 39.9 (C-8), 41.1, 42.7 and 42.8 (C-4, C-12 and $SOCH_3$), 55.6 (C-10), 61.1 (C-11), 65.6 (C-16), 68.8 (C-6), 70.4 (C-7), 71.3 (C-13), 73.9 (C-5), 98.5 (C-2), 119.4 (C-4'), 131.5 (C-5'), 136.5 (C-3'), 148.3 (C-6'), 169.0 (C-2'), 178.3 (C-3), and 197.2 (C-1); m/z (FAB, thioglycerol) 491 (MNa^+) and 470 (MH^+). The spectra indicated that the compound was a mixture of sulphoxide isomers, and essentially in the enolic form.

Example 24

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphonylpyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

The product from 22c (0.235g, 0.35mmol) was dissolved in dichloromethane (15ml), saturated sodium hydrogen carbonate (1.5ml) and water (3ml) added, and the mixture stirred while 3-chloroperbenzoic acid (ca.95%, 0.140g, 0.77mmol) was added. Stirring was continued for seven hours, then water added and the mixture extracted with

dichloromethane (x3). The combined organic extracts were dried and evaporated. The crude material was purified by column chromatography, on silica (10g), eluting with 25-40% ethyl acetate in hexane, to give the pure product (0.097g, 40%).

This material was deprotected using the method described in 5c, to give the title compound (0.037g, 57%); υ_{max} (KBr) 3490, 1623, 1307, 1163, 1103, 1060, and 778cm^{-1}; λ_{max} (EtOH) 320nm (ε_m 14,012); δ_H ($CDCl_3/CD_3OD$) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.22 (3H, d, J 6.4Hz, 14-H_3), 3.29 (3H, S, SO_2CH_3), 6.38 (1H, S, 2-H), 8.18 (1H, d, J 8.2Hz, 3'-H), 8.45 (1H, dd, J 8.2 and 2.0Hz, 4'-H), and 9.16 (1H, d, J 2.0Hz, 6'-H); m/z 485 (M^+, 0.1%), 135 (70), and 122 (100); m/z (FAB, thioglycerol) 498 (MNa^+) and 486 (MH^+). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 25

3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yll-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) N-Methoxy,N-methyl-2-chloropyridine-5-carboxamide

2-Chloropyridine-5-carboxylic acid (1.576g, 10mmol) was dissolved in dry THF (100ml), cooled in an ice-bath, then triethylamine (1.5ml, 11mmol) added, followed by iso-butylchloroformate (1.3ml, 10mmol). The mixture was stirred for 3/4h, then N,O-dimethylhydroxylamine (ex hydrochloride salt, 15mmol) in dichloromethane (70ml) was added. After stirring for 1 3/4h, the mixture was diluted with dichloromethane, washed with water, aqueous sodium hydrogen carbonate, and brine, dried and evaporated. The crude product was purified by column chromatography, on silica (25g), eluting with 40% ethyl acetate in hexane, to give the title compound (1.280g, 64%); δ_H ($CDCl_3$) 3.35 and 3.55 (6H, 2s, 2 x CH_3), 7.35 (1H, d, J 8Hz, 3'-H), 8.0 (1H, dd, J 8 and 2Hz, 4'-H), and 8.7 (1H, d, J 2Hz, 6'-H).

b) 2-Chloropyridine-5-carboxaldehyde

The product from 25a (1.25g, 6.23mmol) was dissolved in dry

dichloromethane (25ml), cooled to -70°C, and treated dropwise with diisobutylaluminium hydride (1.0M in toluene, 9.3ml, 9.3mmol). After stirring for 1h at -70°C, the reaction was quenched with methanol and saturated sodium sulphate solution. The mixture was filtered, the phases separated, the organic washed with brine, dried and evaporated. The crude product was purified by column chromatography, on silica (18g), eluting with 20% ethyl acetate in hexane, to give the title compound (0.743g, 84%); m.p.80-81°C; found C, 50.86; H, 2.60; N, 9.85; Cl, 24.83%. C_6H_4ClNO requires C, 50.91; H, 2.85; N, 9.89; Cl, 25.05%; υ_{max} (CH_2Cl_2) 1713, 1584, 1560, 1349, 1102, and 837cm^{-1}; δ_H ($CDCl_3$) 7.52 (1H, d, J 8.3Hz, 3'-H), 8.15 (1H, dd, J 2.3 and 8.3Hz, 4'-H), 8.87 (1H, d, J 2.3Hz, 6'-H), and 10.11 (1H, s, CHO); m/z 141/143 (M^+, 75 and 25%), 140/142 (100 and 37), and 112/114 (54 and 18). (Found: M^+, 140.9981. C_6H_4ClNO requires M, 140.9981).

c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-chloropyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-chloropyridine-5-carboxaldehyde (0.311g, 2.2mmol) were reacted to give the title compound (0.910g, 69%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.16-5.24 (1H, m, 1-H), 7.32 (1H, d, J 8.3Hz, 3'-H), 7.71 (1H, dt, J 8.3 and 2.3Hz, 4'-H), and 8.37 (1H, d, J 2.3Hz, 6'-H); m/z 660 (MH^+, 3%), 129 (45), 117 (77), and 73 (100); m/z (FAB, 3-NOBA/Na) 682 (MNa^+) and 660 (MH^+). (Found: MH^+, 660.2967. $C_{30}H_{55}ClNO_7Si_3$ requires M, 660.2978).

d) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 25c (0.880g, 1.33mmol) in benzene (40ml) was reacted with manganese dioxide (1.5g) for 3h, to give the title compound (0.442g, 50%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 6.24 (1H, s, 2-H), 7.42 (1H, d, J 8.4Hz, 3'-H), 8.13 (1H, d, J 8.4 and 2.4Hz, 4'-H), and 8.85 (1H, d, J 2.4Hz, 6'-H); m/z 657 (M^+, 0.3%), 117 (70), and 73 (100).

(Found: M+, 657.2747. $C_{30}H_{52}ClNO_7Si_3$ requires M, 657.2740). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

e) 3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 25d (0.420g, 0.64mmol) was deprotected to give the title compound (0.223g, 79%); υ_{max} (KBr) 3443, 1589, 1452, 1303, 1110, 1057, and 1015cm^{-1}; λ_{max} (EtOH) 316nm (ε_m 15,694); δ_H ($CDCl_3/CD_3OD$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.4Hz, 14-H_3), 6.33 (s, 2-H, partly exchanged), 7.50 (1H, d, J 8.4Hz, 3'-H), 8.20 (1H, dd, J 8.4 and 2.4Hz, 4'-H), and 8.86 (1H, d, J 2.4Hz, 6'-H); δ_C ($CDCl_3/CD_3OD$) 11.3 (C-17), 19.2 (C-14), 31.0 (C-9), 39.4 (C-8), 41.5 (C-4), 41.8 (C-12), 55.0 (C-10), 59.9 (C-11), 64.8 (C-16), 67.7 (C-6), 69.4 (C-13), 73.3 (C-7), 76.9 (C-5), 97.2 (C-2), 123.9 (C-3'), 129.1 (C-5'), 136.8 (C-4'), 147.7 (C-6'), 153.8 (C-2'), 177.8 (C-3), and 195.2 (C-1); m/z 441 (M+, 3%), 140/142 (100/35), and 69 (94). (Found: M+, 441.1559. $C_{21}H_{28}ClNO_7$ requires M, 441.1554). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 26

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-hydroxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 5-Triethylsilyloxymethylfuran-2-carboxaldehyde

5-Hydroxymethylfuran-2-carboxaldehyde (0.631g, 5mmol) was dissolved in dry dichloromethane (10ml), cooled in an ice-bath, and triethylamine (1.0ml, 7mmol) added followed by triethylchlorosilane (1.0ml, 6mmol). After stirring for 3/4h, the mixture was evaporated. The residue was purified by column chromatography, on silica (17g), eluting with 10% ethyl acetate in hexane, to give the title compound (1.194g, 99%); δ_H ($CDCl_3$) 0.55-0.8 (6H, m, 3 x CH_2), 0.85-1.15 (9H, m, 3 x CH_3), 4.65 (2H, s, CH_2O), 6.4 and 7.1 (2H, 2d, J 4Hz, 3 and 4-H), and 9.5 (1H, s, CHO).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(5-triethylsilyloxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 5-triethylsilyloxymethylfuran-2-carboxaldehyde (0.529g, 2.2mmol) were reacted to give the title compound (1.000g, 66%); δ_H ($CDCl_3$) inter alia 0.62 (6H, br q, 3 x CH_2), 0.86-1.0 (12H, m, 17-H_3 and 3 x CH_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.61 (2H, s, OCH_2), 5.13-5.20 (1H, m, 1-H), 6.19 and 6.21 (2H, 2d, J 3.2Hz, 3' and 4'-H); m/z (FAB, 3-NOBA/Na) 781 (MNa^+).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(5-triethylsilyloxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 26b (0.975g, 1.28mmol) in benzene (70ml) was reacted with manganese dioxide (4.1g) for 3 1/2h to give the title compound (0.395g, 41%); δ_H ($CDCl_3$) inter alia 0.65 (6H, br q, 3 x CH_2), 0.86-1.01 (12H, m, 17-H_3 and 3 x CH_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 4.70 (2H, s, OCH_2), 6.14 (1H, s, 2-H), 6.41 (1H, d, J 3.5Hz, 4'-H), and 7.10 (1H, d, J 3.5Hz, 3'-H); m/z 756 (M^+, 2%), 117 (100), and 73 (98). (Found: M^+, 756.3949. $C_{36}H_{68}O_9Si_4$ requires M, 756.3940). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-hydroxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 26c (0.386g, 0.5mmol) was completely deprotected to give the title compound (0.153g, 72%); υ_{max} (KBr) 3411, 1618, 1209, 1101, and 1020cm^{-1}; λ_{max} (EtOH) 330nm (ε_m 19,562); δ_H ($CDCl_3/CD_3OD$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.4Hz, 14-H_3), 4.62 (2H, s, OCH_2), 6.18 (s, 2-H, partly exchanged), 6.47 (1H, d, J 3.5Hz, 4'-H), and 7.16 (1H, d, J 3.5Hz, 3'-H); δ_C ($CDCl_3/CD_3OD$) 12.3 (C-17), 20.4 (C-14), 31.5 (C-9), 39.6 (C-8), 40.7 (C-4),

42.5 (C-12), 55.6 (C-10), 56.9 (OCH_2), 60.9 (C-11), 65.4 (C-16), 68.4 (C-6), 70.1 (C-7), 70.7 (C-13), 73.9 (C-5), 96.7 (C-2), 110.0 (C-4'), 117.1 (C-3'), 149.4 (C-2'), 158.9 (C-5'), 175.4 (C-3), and 190.0 (C-1); m/z 426 (M^+, 1%), 140 (100), 125 (92), and 69 (90). (Found: M^+, 426.1900. $C_{21}H_{30}O_9$ requires M, 426.1890). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 27

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-nitrothien-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-nitrothien-4-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-nitrothiophene-4-carboxaldehyde (0.346g, 2.2mmol) were reacted to give the title compound (0.390g, 69%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 5.11-5.21 (1H, m, 1-H), 7.46-7.50 and 7.87-7.91 (2H, m, 3' and 5'-H); m/z (FAB, 3-NOBA/Na) 698 (MNa^+).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-nitrothien-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-tri-methylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 27a (0.500g, 0.74mmol) in benzene (35ml) was reacted with manganese dioxide (1.0g) for 4 1/2h to give the title compound (0.186g, 37%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 6.08 (1H, s, 2-H), 8.14 and 8.23 (2H, 2d, J 1.7Hz, 3' and 5'-H); m/z (FAB, thioglycerol) 674 (MH^+); m/z (FAB, 3-NOBA/Na) 718 (M + 2Na-H^+). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-nitrothien-4-yl)

but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran

Using the method described in 5c, the product from 27b (0.170g, 0.25mmol) was deprotected to give the title compound (0.095g, 83%); υ_{max} (KBr) 3423, 1604, 1534, 1506, 1336, 1111, and 1052cm^{-1}; λ_{max} (EtOH) 311nm (ε_m 20,545); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 6.09 (1H, s, 2-H), 8.16 and 8.22 (2H, 2d, J 1.7Hz, 3' and 5'-H); δ_C ($CDCl_3/CD_3OD$) 12.4 (C-17), 20.4 (C-14), 31.9 (C-9), 40.1 (C-8), 42.1 (C-4), 42.7 (C-12), 55.9 (C-10), 61.0 (C-11), 65.8 (C-16), 68.6 (C-6), 70.2 (C-7), 70.6 (C-13), 74.2 (C-5), 98.1 (C-2), 126.7 and 134.5 (C-3' and 5'), 137.8 (C-4'), 152.7 (C-2'), 175.8 (C-3), and 195.1 (C-1); m/z (FAB, thioglycerol) 475 (MNH_4^+) and 458 (MH^+); m/z (FAB, 3-NOBA/Na) 502 (M + 2Na-H^+) and 480 (MNa^+).

Example 28

3R,4R-Dihydroxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) N-Methoxy, N-methyl-2-bromopyridine-5-carboxamide

Using the method described in 25a, 2-bromopyridine-5-carboxylic acid (2.02g, 10mmol) was reacted to give the title compound (1.637g, 67%); δ_H ($CDCl_3$) 3.35 and 3.55 (6H, 2s, 2 x CH_3), 7.55 (1H, d, J 8Hz, 3'-H), 7.9 (1H, dd, J 8 and 2Hz, 4'-H), and 8.7 (1H, d, J 2Hz, 6'-H).

b) 2-Bromopyridine-5-carboxaldehyde

Using the method described in 25b, N-methoxy, N-methyl-2-bromopyridine-5-carboxamide (1.60g, 6.53mmol) was reacted to give the title compound (1.042g, 86%); m.p.103.5-104°C (chloroform/hexane); found C, 38.72; H, 2.09; N, 7.53; Br, 42.62%. C_6H_4BrNO requires C, 38.74; H, 2.17; N, 7.53; Br. 42.96%; δ_H [$(CD_3)_2CO$] 7.8 (1H, d, J 8Hz, 3'-H), 8.15 (1H, dd, J 8 and 2Hz, 4'-H), 8.85 (1H, d, J 2Hz, 6'-H), and 10.15 (1H, s, CHO).

c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-bromopyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-bromopyridine-5-carboxaldehyde (0.409g, 2.2mmol) were reacted to give the title compound (0.729g, 52%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.13-5.22 (1H, m, 1-H), 7.47 (1H, d, J 8.2Hz, 3'-H), 7.58-7.64 (1H, m, 4'-H), and 8.35 (1H, d, J 2.3Hz, 6'-H); m/z (NH_3, DCI) 706/704 (MH^+, 10%), 186/188 (50), 108 (50), and 90 (100).

d) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 28c (0.721g, 1.02mmol) in benzene (40ml) was reacted with manganese dioxide (1.44g) for 2½ hours to give the title compound (0.320g, 45%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 6.24 (1H, s, 2-H), 7.59 (1H, d, J 8.3Hz, 3'-H), 8.01 (1H, dd, J 8.3 and 2.5Hz, 4'-H), and 8.82 (1H, d, J 2.5Hz, 6'-H); m/z 701/703 (M^+, 1%), 409/411 (5), 117 (100), and 73 (97). (Found: M^+, 701.2232. $C_{30}H_{52}BrNO_7Si_3$ requires M, 701.2235). The ^1H n.m.r. spectrum indicated that the compound was essentially in the enolic form.

e) 3R,4R-Dihydroxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 28d (0.310g, 0.44mmol) was deprotected to give the title compound (0.090g, 42%); m.p.133-134°C; found C, 51.53; H, 5.85; N, 2.94%; $C_{21}H_{28}BrNO_7$ requires C, 51.86; H, 5.80; N, 2.88%; υ_{max} (KBr) 3435, 1576, 1452, 1096, 1057, and 1013cm^{-1}; λ_{max} (EtOH) 313 (ε_m 18,198) and 248nm (8,079); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 6.47 (1H, s, 2-H), 7.73 (1H, d, J 8.5Hz, 3'-H), 8.16 (1H, dd, J 8.5 and 2.4Hz, 4'-H), and 8.86 (1H, d, J 2.4Hz, 6'-H); δ_C (CD_3OD) 12.3 (C-17),

20.3 (C-14), 33.0 (C-9), 41.8 (C-8), 43.2 (C-4), 43.7 (C-12), 56.9 (C-10), 61.2 (C-11), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.4 (C-5), 99.1 (C-2), 129.6 (C-3'), 131.5 (C-5'), 138.4 (C-4'), 146.4 (C-2'), 149.8 (C-6'), 179.7 (C-1), and 197.8 (C-3); m/z (NH_3 DCI) 486/488 (MH^+, 30%), 200/202 (35), and 122 (100); m/z 485/487 (M^+, 2%), 226/228 (48), 200/202 (70), 184/186 (80), 71 (85), and 69 (100). (Found: M^+, 485.1022. $C_{21}H_{28}BrNO_7$ requires M, 485.1049). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 29

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-methoxyfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 5-Methoxyfuran-2-carboxaldehyde

n-Butyllithium (1.5M, 7.3ml, 11mmol) was added slowly to diisopropylamine (1.5ml, 10.5mmol) in THF (20ml) at -30°C. Stirred for 10 mins, cooled to -70°C, and 2-methoxyfuran (0.981g, 10mmol) in THF (8ml) added slowly. After stirring for ½h dimethylformamide (2.4ml, 30mmol) was added, and the mixture stirred for a further 1h. After quenching with saturated aqueous ammonium chloride, the mixture was extracted with dichloromethane (x2). The combined organic extracts were washed with brine, dried and carefully evaporated. The residue was purified twice by flash chromatography, eluting with ether/hexane mixtures, to give the title compound (0.463g, 37%); δ_H ($CDCl_3$) 4.05 (3H, s, OCH_3), 5.55 (1H, d, J 4Hz, 4-H), 7.3 (1H, d, J 4Hz, 3-H), and 9.35 (1H, s, CHO).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(5-methoxyfuran-2-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 5-methoxyfuran-2-carboxaldehyde (0.29g, 2.2mmol) were reacted to give the title compound (1.058g, 82%); δ_H ($CDCl_3$) inter alia 0.9 (3H, d, J 7Hz, 17-H_3), 1.2 (3H, d, J 6Hz, 14-H_3), 3.8 (OCH_3), 4.9-5.15 (2H,

m, 1-H and 4'-H), and 6.1 (1H, d, J 4Hz, 3'-H). The product was unstable, and readily dehydrated.

c) 3R,4R-Bistrimethylsylyloxy-2S-[2,4-dioxo-4-(methoxy-furan-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 29b (1.01g, 1.57mmol) in benzene (40ml) was reacted with manganese dioxide (3.0g) for 4 hours to give the title compound (0.159g, 16%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.96 and 3.97 (OCH_3), 5.39 (0.8H, d, J 3.6Hz) and 5.41 (0.2H, d, J 3.8Hz, 4'-H), 5.98 (0.8H, s, 2-H), and 7.14 (0.8H, d, J 3.6Hz) and 7.23 (0.2H, d, J 3.8Hz, 3'-H); m/z (NH_3 DCI) 643 (MH^+, 22%) and 90 (100); m/z 643 (MH^+, 3%), 125 (50), 117 (100), and 73 (72). (Found: MH^+, 643.3140. $C_{30}H_{55}O_9Si_3$ requires MH^+, 643.3154).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-methyoxyfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 29c (0.146g, 0.23mmol) was deprotected to give the title compound (0.080g, 82%); υ_{max} (KBr) 3432, 1718, 1627, 1523, 1426, and 1042cm^{-1}; λ_{max} (EtOH) 347nm (ε_m 16,692); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 3.97 (OCH_3), 5.59 (1H, d, J 3.7Hz, 4'-H), 6.01 (1H, s, 2-H), and 7.29 (1H, d, J 3.7Hz, 3'-H); δ_C (CD_3OD) 12.3 (C-17), 20.4 (C-14), 33.0 (C-9), 40.6 (C-4), 41.7 (C-8), 43.8 (C-12), 56.9 (C-10), 58.9 (OCH_3), 61.3 (C-11), 66.5 (C-16), 69.7 (C-6), 70.8 (C-13), 71.5 (C-7), 74.4 and 75.5 (C-5), 85.6 (C-4'), 96.7 (C-2), 122.3 (C-3'), 142.2 (C-2'), 166.4 (C-5'), 178.2 (C-1), and 187.0 (C-3); m/z (NH_3 DCI) 427 (MH^+, 100%); m/z 426 (M^+, 3%), 140 (60), and 125 (100). (Found: M^+, 426.1892. $C_{21}H_{30}O_9$ requires M, 426.1890). The n.m.r. spectra indicated that the title compound was mainly in the enolic form, but contained 20-40% of the diketone.

Example 30

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)-

pyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-(Piperidin-1-yl)pyrimidine-5-carboxaldehyde

5-Bromo-2-chloropyrimidine was converted to 5-bromo-2-(piperidin-1-yl)pyrimidine using the method of Nasielski et al (Tetrahedron 1972, 28, 3767). Using the method described in 21a, 5-bromo-2-(piperidin-1-yl)pyrimidine (3.63g, 15mmol) was converted to the title compound (1.23g, 43%); δ_H ($CDCl_3$) 1.5-1.8 (6H, m, 3',4',5'-CH_2), 3.8-4.1 (4H, m, 2 x NCH_2), 8.65 (2H, s, 4' and 6'-H), and 9.7 (1H, s, CHO).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(2-(piperidin-1-yl)pyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-(piperidin-1-yl)pyrimidine-5-carboxaldehyde (0.421g, 2.2mmol) were reacted to give the title compound (1.140g, 80%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 1.48-1.90 (9H, m, 9-H_2, 8-H, 3 x CH_2), 3.72-3.98 (7H, m, 16,13,7-H and 2 x NCH_2), 4.98-5.08 (1H, m, 1-H), and 8.30 (2H, s, 4' and 6'-H); m/z (NH_3 DCI) 710 (MH^+, 20%), 192 (100), and 91 (82); m/z 710 (MH^+, 3%), 709 (M^+, 2), 191 (70), 129 (82), and 117 (100). (Found: M^+, 709.3981. $C_{34}H_{63}N_3O_7Si_3$ requires M, 709.3974).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)pyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 30b (1.12g, 1.58mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 4 hours to give the title compound (0.681g, 61%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 1.5-1.9 (9H, m, 9-H_2, 8-H, 3 x CH_2), 3.7-3.95 (7H, m, 16,13,7-H and 2 x NCH_2), 6.06 (1H, s, 2-H), and 8.77 (2H, s, 4' and 6'-H); m/z (NH_3 DCI) 708 (MH^+, 7%), 147 (97), 91 (100), and 74 (95); m/z 707 (M^+, 1%), 190 (98), and 73 (100). (Found: M^+, 707.3820. $C_{34}H_{61}N_3O_7Si_3$ requires M, 707.3817). The $_1H$ n.m.r.

spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)-pyrimidine-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 30c (0.655g, 0.92mmol) was deprotected to give the title compound (0.388g, 85%); found C, 60.72; H, 7.75; N, 8.49%. $C_{25}H_{37}N_3O_7$ requires C, 61.08; H, 7.59; N, 8.55%; υ_{max} (KBr) 3466, 1609, 1541, 1269, 1254, and 803cm^{-1}; λ_{max} (EtOH) 348nm (ε_m 33,937); δ_H ($CDCl_3/CD_3OD$) inter alia 0.93 (3H, d, J 7.1Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 1.58-1.90 (8H, m, 9-H_2 and 3 x CH_2), 3.74-4.0 (8H, m, 5,7,13,16-H and 2 x NCH_2), 6.08 (1H, s, 2-H), and 8.77 (2H, s, 4' and 6'-H); δ_C ($CDCl_3/CD_3OD$) 12.4 (C-17), 20.4 (C-14), 24.8 (C-4"), 26.0 (C-3" and 5"), 31.9 (C-9), 40.0 (C-8), 41.3 (C-4), 42.7 (C-12), 45.4 (C-2" and 6"), 55.9 (C-10), 61.1 (C-11), 65.8 (C-16), 68.7 (C-6), 70.2 (C-7), 70.6 (C-13), 74.3 (C-5), 95.6 (C-2), 116.3 (C-5'), 158.0 (C-4' and 6'), 161.9 (C-2'), 182.1 (C-1), and 190.8 (C-3); m/z 491 (M^+, 7%), 232 (36), 206 (54), 204 (56), and 190 (100). (Found: M^+, 491.2602. $C_{25}H_{37}N_3O_7$ requires M, 491.2630). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 31

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methyl-2-methylthio-imidazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) Ethyl 1-methyl-2-methylthioimidazole-4-carboxylate

Ethyl 2-mercaptoimidazole-4(5)-carboxylate (10.0g, 58mmol) was dissolved in dry DMF (200ml), and sodium hydride (80% in oil, 3.5g, 116mmol) added slowly with cooling. The mixture was stirred for 1h under argon, cooled in an ice bath, and methyl iodide (14.4ml, 232mmol) added. The reaction was then stirred overnight, diluted with water (200ml) and extracted with ethyl acetate (6 x 100ml). The combined organic extracts were washed with brine, dried and evaporated. The crude product was

separated by flash chromatography eluting with 32-44% ethyl acetate in hexane, to give (a) the 1,2,5-isomer (3.742g, 32%), and (b) the title compound (4.261g, 37%); δ_H ($CDCl_3$) 1.35 (3H, t, J 7Hz, CH_3), 2.6 (3H, s, SCH_3), 3.6 (3H, s, NCH_3), 4.3 (2H, q, J 7Hz, CH_2), and 7.55 (1H, s, 5-H). The assignments of the structures were confirmed by n.O.e. studies.

b) 1-Methyl-2-methylthioimidazole-4-carboxaldehyde

Ethyl 1-methyl-2-methylthioimidazole-4-carboxylate (1.97g, 9.8mmol) was dissolved in dry THF (80ml) under argon, then diisobutylaluminium hydride (1.0M in toluene, 22ml, 22mmol) was added slowly. The mixture was stirred at room temperature for 1½h, and at reflux for ½h. The reaction was cooled, quenched with methanol (25ml) and saturated sodium sulphate (31ml), and stirred for 15 minutes. The mixture was then filtered, washing well with ethyl acetate, and the filtrate extracted with ethyl acetate (x4). The combined organic extracts were dried and evaporated to give crude 4-hydroxymethyl-1-methyl-2-methylthioimidazole (1.43g, 92%).

This material was dissolved in dry chloroform (70ml), activated manganese dioxide (1.5g) added and the mixture stirred for 30 minutes. Only a little reaction had occurred, so 4A sieves (4g) were added, followed portionwise by more manganese dioxide (3.5g). After stirring overnight the reaction was complete. The mixture was filtered, washing the manganese dioxide thoroughly with chloroform and dichloromethane, and the filtrate evaporated. The residue was purified by column chromatography on silica (38g), eluting with 90-100% ethyl acetate in hexane, to give the title compound as a white solid (1.183g, 84%; 77% overall); υ_{max} (CH_2Cl_2) 1680, 1540, 1320, and 1130cm^{-1}; δ_H ($CDCl_3$) 2.68 (3H, s, SCH_3), 3.65 (3H, s, NCH_3), 7.68 (1H, s, 5-H), and 9.7 (1H, s, CHO).

c) 3R,4R-Bistrimethylsilyloxy-2-[4-hydroxy-4-(1-methyl-2-methylthioimidazol-4-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 1-methyl-2-methylthioimidazole-4-carboxaldehyde were

reacted to give the title compound (1.050g, 78%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 2.57 (3H, s, SCH_3), 3.58 (3H, s, NCH_3), 5.10-5.18 (1H, m, 1-H), and 6.88 (1H, s, 5'-H); m/z (NH_3 DCI) 675 (MH^+, 40%) and 157 (100); m/z 674 (M^+, 1%), 156 (50), 129 (62), and 117 (100). (Found: M^+, 674.3267. $C_{30}H_{58}N_2O_7SSi_3$ requires M, 674.3273).

d) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(1-methyl-2-methylthioimidazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 31c (1.03g, 1.50mmol) in benzene (70ml) was reacted with manganese dioxide (2.0g) for 2 hours to give the title compound (0.656g, 64%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 2.66 (3H, s, SCH_3), 3.62 (3H, s, NCH_3), 6.44 (1H, s, 2-H), and 7.55 (1H, s, 5'-H); m/z (NH_3 DCI) 673 (MH^+, 100%); m/z 673 (MH^+, 2%), 672 (M^+, 1%), 197 (30), 155 (53), 117 (50), and 73 (100). (Found: M^+, 672.3125. $C_{30}H_{56}N_2O_7SSi_3$ requires M, 672.3116).

e) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methyl-2-methyl-thioimidazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 31d (0.240g, 0.36mmol) was deprotected to give the title compound (0.140g, 85%); υ_{max} (KBr) 3426, 1616, 1451, 1379, 1332, 1135, 1108, and 1055cm^{-1}; λ_{max} (EtOH) 328nm (ε_m 17,229); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.1Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 2.66 (3H, s, SCH_3), 3.64 (3H, s, NCH_3), 6.44 (1H, s, 2-H), and 7.58 (1H, s, 5'-H); δ_C ($CDCl_3$) 12.6 (C-17), 16.1 (SCH_3), 20.7 (C-14), 31.6 (C-9), 33.6 (NCH_3), 39.5 (C-8), 42.2 (C-4), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 69.1 (C-6), 70.3 (C-7), 71.2 (C-13), 73.9 (C-5), 96.9 (C-2), 126.3 (C-5'), 137.9 (C-4'), 145.7 (C-2'), 178.5 (C-1), and 193.2 (C-3); m/z (NH_3 DCI) 457 (MH^+, 100%); m/z 456 (M^+, 2%), 170 (75) and 155 (100). (Found: M^+, 456.1922. $C_{21}H_{32}N_2O_7S$ requires M, 656.1930). The ^1H n.m.r. spectrum indicated that the title compound was mainly in the enolic form (17% of the diketone present).

Example 32

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-methoxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (0.725g, 1.4mmol) and 2-methoxybenzaldehyde (218mg, 1.68mmol) were reacted to give the title compound (600mg, 65%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.83 (3H, s, OMe), 4.08-4.19 (1H, m, H-5), 5.36-5.50 (1H, m, H-1), 6.85 (1H, d, J 8.1Hz, H-3'), 6.98 (1H, t, J 7.2Hz, H-5'), 7.24 (1H, dt, J 1.6 and 8.0Hz, H-4'), 7.48 (1H, d, J 7.4Hz, H-6'). (Found: M^+, 654.3456. $C_{32}H_{58}O_8Si_3$ requires M, 654.3440).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 32a (600mg, 0.92mmol) in benzene (50ml) was reacted with manganese dioxide (1.5g) for 3 hours to give the title compound (260mg, 43%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.92 (3H, s, OMe), 6.53 (1H, s, 2-H), 6.96 (1H, d, J 8.3Hz, 3'-H), 7.02 (1H, t, J 7.7Hz, 5'-H), 7.43 (1H, dt, J 1.8 and 8.3Hz, 4'-H), 7.88 (1H, dd, J 1.8 and 7.8Hz, 6'-H). (Found: M^+, 652.3293. $C_{32}H_{56}O_8Si_3$ requires M, 652.3283).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 32b (250mg, 0.38mmol) was deprotected to give the title compound (142mg, 85%); υ_{max} (KBr) 3431, 1718, 1603, 1489cm^{-1}; λ_{max} (EtOH) 326.5nm (ε_m 12,445), 306 (11,456), 253.5 (4,740); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.92 (3H, s, OMe), 6.58 (1H, s, 2-H),

6.97 (1H, d, J 8.3Hz, 3'-H), 7.04 (1H, t, J 7.7Hz, 5'-H), 7.45 (1H, dt, J 1.8 and 8.3Hz, 4'-H), 7.91 (1H, dd, J 1.8 and 7.8Hz, 6'-H); δ_C ($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 39.5 (C-8), 42.8 (C-12), 43.3 (C-4), 55.7 (C-10), 55.7 (ArOMe), 61.3 (C-11), 65.6 (C-16), 69.3 (C-7), 70.3 (C-6), 71.3 (C-13), 73.7 (C-5), 102.4 (C-2), 111.7 (C-5'), 123.4 (C-1'), 130.2 (C-3'), 133.2 (C-6'), 158.6 (C-2'), 180.1 (C-1), 196.7 (C-3). (Found: M$^+$, 437.2164. $C_{23}H_{33}O_8$ requires M, 437.2175). The ^{1}H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 33

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-methylthiophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (2.175g, 4.2mmol) and 4-methylthiobenzaldehyde (0.64ml, 4.8mmol) were reacted to give the title compound (2.12g, 75%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 2.48 (3H, s, ArSMe), 4.05-4.18 (1H, m, 5-H), 5.08-5.20 (1H, m, 1-H), 7.20-7.34 (4H, m, Ar); m/z (FAB) 693 (MNa$^+$).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 33a (2.12g, 3.16mmol) in benzene (150ml) was reacted with manganese dioxide (4.2g) for 2 hours to give the title compound (1.3g, 62%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 2.52 (3H, s, ArSMe), 6.23 (1H, s, 2-H), 7.26 (2H, d, J 8.6Hz, 3',5'-H_2), 7.80 (2H, d, J 8.6Hz, 2',6'-H_2). (Found: M$^+$, 668.3060. $C_{32}H_{56}O_2SSi$ requires M, 668.3055).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-

hexyl)tetrahydropyran

Using the method described in 5c, the product from 33b (250mg, 0.37mmol) was deprotected to give the title compound (144mg, 85%); υ_{max} (KBr) 3425, 1591, 1488, 1436, 1267cm^{-1}; λ_{max} (EtOH) 337nm (ε_m 27,090), 239 (5,680); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 2.35 (3H, s, ArSMe), 6.23 (1H, s, 2-H), 7.26 (2H, d, J 8.6Hz, 3',5'-H_2), 7.80 (2H, d, J 8.6Hz, 2',6'-H_2); δ_C ($CDCl_3$) 11.9 (C-17), 14.5 (ArSMe), 20.0 (C-14), 31.5 (C-9), 39.6 (C-8), 41.9 (C-4), 42.3 (C-12), 55.5 (C-10), 60.7 (C-11), 65.4 (C-16), 68.3 (C-7), 69.9 (C-6), 70.3 (C-13), 73.8 (C-5), 96.6 (C-2), 125.1 (C-3',5'), 127.2 (C-2',6'), 130.5 (C-1'), 144.9 (C-4'), 181.9 (C-1), 194.1 (C-3). (Found: M^+, 452.1867. $C_{23}H_{32}O_7S$ requires M 452.1869). The ^{1}H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 34

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylsulphinyl-phenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)-tetrahydropyran

Using the method described in 23, the product from 33c (200mg, 0.3mmol) was reacted to give the pure product (175mg, 85%). This material was deprotected using the method described in 5c to give the title compound (154mg, 45%); υ_{max} (KBr) 3417, 1600, 1560, 1451, 1292cm^{-1}; λ_{max} (EtOH) 317nm (ε_m 17,420), 225 (7,480); δ_H ($CDCl_3$) inter alia, 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 2.77 (3H, s, ArS(O)Me), 6.30 (1H, s, 2-H), 7.72 (2H, d, J 8.4Hz, 3',5'-H_2), 8.03 (2H, d, J 8.4Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.6 (C-14), 31.6 (C-9), 39.6 (C-8), 42.8 (C-12 and C-4), 43.6 (ArS(O)Me), 55.6 (C-10), 61.1 (C-11), 65.6 (C-16), 66.8 (C-7), 70.3 (C-6), 71.2 (C-13), 73.7 (C-5), 98.0 (C-2), 123.9 (C-3',5'), 128.0 (C-2',6'), 137.2 (C-1'), 149.5 (C-4'), 180.1 (C-1), 196.7 (C-3); m/z (FAB) 491 (MNa^+), 469 (MH^+). The ^{1}H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 35

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylsulphonyl-phenyl)-

but-1-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)-tetrahydropyran

Using the method described in 24, the product from 34c (200mg, 0.3mmol) was reacted to give the pure product (155mg, 74%). This material was deprotected using the method described in 5c to give the title compound (90mg, 92%); υ_{max} (KBr) 3495, 3438, 1622, 1602cm^{-1}; λ_{max} (EtOH) 317.5nm (ε_m 14,510), 239 (8,540); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 3.13 (3H, s, $ArSO_2Me$), 6.37 (approx. 1H, s, exch, 2-H), 7.92-8.17 (4H, m, Ar); m/z (FAB) 485 (MH^+). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 36

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-cyanophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3-cyanophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, 3-cyanobenzaldehyde (4.19mg, 3.2mmol) was reacted to give the title compound (1.46g, 80%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 5.13-5.26 (1H, m, 1-H), 7.48-7.62 (3H, m), 7.70 (1H, s, 2'-H); m/z (NH_3 DCI), 667 (MNH_4^+, 50%), 650 (MH^+, 10%), 536 (100).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-cyanophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 36a (1.45g, 2.23mmol) in benzene (120ml) was reacted with manganese dioxide (2.18g) for 3½h to give the title compound (574mg, 40%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 6.26 (1H, s, 2-H), 7.58 (1H, t, J 7.8Hz, 5'-H), 7.79 (1H, dd, J 1.2 and 7.7Hz, 4'-H), 8.10 (1H, dd, J 1.0 and

6.7Hz, 6'-H), 8.16 (1H, d, J 1.4Hz, 2'-H); m/z 648 (MH^+).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-cyanophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method decribed in 5c, the product from 36b (550mg, 0.85mmol) was deprotected to give the title compound (315mg, 86%); υ_{max} (KBr) 3439, 2232, 1610, 1570, 1452cm^{-1}; λ_{max} (EtOH) 312.5nm (ε_m 14,620), 239.5 (9,990); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3) 1.22 (3H, d, J 6.3Hz, 14-H_3), 6.27 (1H, s, 2-H), 7.60 (1H, t, J 7.8Hz, 5'-H), 7.80 (1H, d, with further fine coupling, J 7.8Hz, 4'-H), 8.10 (1H, d, with further fine coupling, J 8.0Hz, 6'-H), 8.16 (1H, d, J 1.2Hz, 2'-H); δ_C ($CDCl_3$) 12.9 (C-17), 21.0 (C-14), 31.8 (C-9), 39.9 (C-8), 42.9 (C-4), 43.0 (C-12), 55.8 (C-10), 61.4 (C-11), 65.8 (C-16), 69.0 (C-6), 70.5 (C-13), 71.5 (C-7), 74.1 (C-5), 98.0 (C-2), 113.3 (C-1'), 118.2 (C-3'), 129.8 (C-2'), 130.9 (C-4'), 131.3 (C-6'), 135.4 (C-5'), 136.0 (CN), 179.6 (C-3), 196.9 (C-1). (Found: M^+ 431.1949. $C_{23}H_{29}NO_7$ requires M 431.1944). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 37

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-trifluoromethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-trifluoromethoxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilymonone (1.45mg, 2.8mmol) and 4-trifluoromethoxybenzaldehyde (608mg, 3.2mmol) were reacted to give the title compound (1.52g, 76%); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.1Hz, 17-H_3), 1.23 (3H, d, J 6.4Hz, 14-H_3), 4.07-4.18 (1H, m, 5-H), 5.10-5.22 (1H, m, 1-H), 7.18-7.28 (2H, m, 3',5'-H_2), 7.38-7.49 (2H, m, 2',6'-H_2); m/z (NH_3 DCI) 726 (MNH_4^+, 30%), 90 (100%). [Found: MH^+, 709.3239. $C_{31}H_{55}O_8F_3Si_3$ requires MH, 709.3235.]

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-trifluoromethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 37a (1.5g, 2.15mmol) in benzene (120ml) was reacted with manganese dioxide (3g) for 1½ hours to give the title compound (772mg, 51%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 4.08-4.20 (1H, m, 5-H), 6.24 (1H, s, 2-H), 7.22-7.34 (2H, m, 3',5'-H_2), 7.93 (2H, d, J 8.8Hz, 2',6'-H_2); m/z 707 (MH^+, 8%), 73 (100). [Found: MH, 707.3072. $C_{31}H_{59}O_8F_3Si_3$ requires MH, 707.3079.]

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-trifluoromethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 37b (750mg, 1.06mmol) was deprotected to give the title compound (350mg, 74%); υ_{max} (KBr) 3496, 1624, 1583, 1506, 1441cm^{-1}; λ_{max} (EtOH) 311nm (ε_m 16,860), 243.5 (6730); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 6.24 (1H, s, 2-H), 7.24-7.35 (2H, m, 3',5'-H_2), 7.92 (2H, d, J 8.8Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.7 (C-4), 42.9 (C-12), 55.7 (C-10), 65.7 (C-16), 69.0 (C-7), 70.3 (C-6), 71.4 (C-13), 73.9 (C-5), 97.5 (C-2), 120.6 (C-3',5'), 129.0 (C-2',6'), 132.9 (C-1'), 152.2 (C-4'), 180.9 (C-1), 196.0 (C-3); m/z 491 (MH^+, 30%), 189 (100). [Found: MH^+, 491.1893. $C_{23}H_{30}O_8F_3$ requires MH, 491.1893.] The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 38

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-fluorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.45g, 2.8mmol) and 4-fluorobenzaldehyde (0.34ml, 3.2mmol) were reacted to give the title compound (1.5g, 83%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 4.08-4.17 (1H, m, 5-H), 5.11-5.22 (1H, m, 1-H), 7.03 (2H, t, J 8.7Hz, 3',5'-H_2), 7.30-7.41 (2H, m, 2',6'-H_2); m/z (NH_3 DCI) 660 (MNH_4^+, 52%), 643 (MH^+, 15), 90 (100). [Found: MH^+, 643.3811. $C_{31}H_{55}O_7FSi_3$ requires MH, 643.3318.]

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 38a (1.5g, 2.34mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 1½ hours to give the title compound (890mg, 59%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 4.06-4.18 (1H, m, 5-H), 6.22 (1H, s, 2-H), 7.13 (2H, t, J 8.7Hz, 3',5'-H_2), 7.91 (2H, dd, J 5.4 and 8.7Hz, 2',6'-H_2); m/z (NH_3 DCI) 641 (MH^+). [Found: MH^+, 641.3167. $C_{31}H_{54}O_7FSi_3$ requires MH, 641.3161.]

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 38b (400mg, 0.625mmol) was deprotected to give the title compound (215mg, 81%); υ_{max} (KBr) 3427, 1603, 1505, 1452cm^{-1}; λ_{max} (EtOH) 310nm (ε_m 15,800), 248.5 (5,785); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.1Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 6.22 (1H, s, 2-H), 7.13 (2H, t, J 8.7Hz, 3',5'-H_2), 7.90 (2H, dd, J 5.4 and 8.7Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.8 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.6 (C-4), 42.9 (C-12), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 69.0 (C-7), 70.3 (C-6), 71.4 (C-13), 73.9 (C-5), 97.2 (C-2), 115.8 (d, J 23Hz, C-3',5'), 129.6 (d, J 9Hz, C-2',6'), 130.7 (d, J 3Hz, C-1'), 165.4 (d, J 252Hz, C-4'), 181.8 (C-1), 195.1 (C-3); m/z (NH_3 DCI) 425 (MH^+, 15%), 79 (100). [Found: MH^+, 425.1968. $C_{22}H_{30}O_7F$ requires MH, 425.1976.] The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 39

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-hydroxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-Triethylsilyloxybenzaldehyde

A suspension of 4-hydroxybenzaldehyde (610mg, 5mmol) in dichloromethane (30ml) at 5° under argon was treated with triethylamine (0.84ml, 6mmol) followed by triethylsilyl chloride (1ml, 6mmol). After 30 minutes ether was added and the mixture filtered through Kieselguhr. The filtrate was washed with brine, dried ($MgSO_4$) and evaporated to give the title aldehyde (1.1g) as an orange oil; δ($CDCl_3$) 0.55-1.42 (15H, m), 6.96 (2H, d, J 9Hz), 7.83 (2H, d, J 9Hz), 9.95 (1H, s). This material was sufficiently pure for further synthetic manipulations.

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-triethylsilyloxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, 4-triethylsilyloxy-benzaldehyde (520mg, 2mmol) and tris trimethylsilylmonone (1.04g, 2mmol) were reacted to give the title compound (1.2g, 80%); δ_H ($CDCl_3$) inter alia 0.66-0.82 (6H, m, $Si(CH_2CH_3)_3$), 0.89 (3H, d, J 7.0Hz, 17-H_3), 0.99 (9H, t, J 7.4Hz, $Si(CH_2CH_3)_3$), 4.08-4.17 (1H, m, 5-H), 5.05-5.16 (1H, m, 1-H), 6.84 (2H, d, J 8.5Hz, 3',5'-H_2), 7.18-7.27 (2H, m, 2',6'-H_2); m/z (FAB; 3-NOBA/Na) 777 (MNa^+, 100%).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-triethylsilyloxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 39b (1.2g) in benzene (70ml) was reacted with manganese dioxide (3.4g) for 3 hours to give the title compound (598mg, 50%); δ_H ($CDCl_3$) inter alia 0.68-0.82 (6H, m, $Si(CH_2CH_3)_3$), 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.00 (9H, t, J 7.4Hz, $Si(CH_2CH_3)_3$), 1.20 (3H, d, J 6.4Hz, 14-H_3), 6.20 (1H, s, 2-H), 6.88 (2H, d, J 8.7Hz, 3',5'-H_2), 7.81 (2H, d, 8.7Hz, 2',6'-H_2); m/z (FAB; 3-NOBA/Na) 775 (MNa^+, 40%), 235 (100%).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-hydroxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c the product from 39c (598mg, 0.8mmol) was deprotected to give the triethylsilylated title compound (264mg). This material was dissolved in tetrahydrofuran (THF) (5ml) and treated with acetic acid (30µl, 0.5mmol) and a solution of tetrabutylammonium fluoride trihydrate in THF (1M, 0.5ml, 0.5mmol). After 20 minutes the mixture was diluted with ethyl acetate and washed with brine, dried, evaporated and chromatographed on silica eluting with dichloromethane/ methanol mixtures to give the title compound containing 25% tetrabutyl ammonium acetate (234mg). This mixture was treated with ethyl acetate (10ml), water (5ml) and nonafluorobutane sulphonate (76mg). The organic phase was separated, washed with brine, dried and evaporated.
Chromatography eluting with dichloromethane/methanol mixtures gave the title compound (168mg) as a solid; ν_{max} (KBr) 3385, 1604, 1508, 1455cm^{-1}; λ_{max} (EtOH) 326nm (ε_m 21,460); δ_H (d_6-acetone) inter alia 0.92 (3H, d, J 7.1Hz, 17-H_3), 1.16 (3H, d, J 6.4Hz, 14-H_3), 6.39 (1H, s, 2-H), 6.95 (2H, d, J 8.8Hz, 3',5'-H_2), 7.90 (2H, d, J 8.8Hz, 2',6'-H_2); δc (d_6-acetone) 12.3 (C-17), 20.8 (C-14), 32.6 (C-9), 41.2 (C-8), 42.3 (C-4), 43.3 (C-12), 55.6 (C-10), 60.4 (C-11), 66.0 (C-16), 69.4 (C-7), 70.1 (C-6), 71.1 (C-13), 75.1 (C-5), 96.7 (C-2), 116.3 (C-3',5'), 127.3 (C-1'), 130.2 (C-2',6'), 162.5 (C-4'), 184.9 (C-1), 194.1 (C-3); m/z 440 (MNH_4^+, 12%), 423 (MH^+, 15%), 181 (100%).

EXAMPLE 40

3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-Allyloxybenzaldehyde

A solution of 4-allyloxybromobenzene (K. Mino et al, Synthesis, 1979, 688) (1.5g, 7.5mmol) in THF (25ml) at -70° under argon was treated with a solution of n-butyllithium in hexane (1.5M, 5ml, 7.5mmol). After 30 minutes the reaction mixture was treated with dimethylformamide (0.88ml, 11.25mmol). After 10 minutes saturated ammonium chloride was

added and the mixture extracted with ethyl acetate. The organic phase was washed with brine, dried, evaporated and chromatographed on silica eluting with ethyl acetate/hexane mixtures to give the title compound (784mg) contaminated with ethyl acetate (16%); δ_H ($CDCl_3$) inter alia 4.61 (1H, dd, J 2,6Hz), 4.93 (1H, dd, J 2,14Hz), 6.71 (1H, dd, J 6,14Hz), 7.12 (2H, d, J 9Hz), 7.88 (2H, d, J 9Hz), 9.93 (1H, s). This material was used in further synthetic transformations.

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-allyloxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, the product from 40a was reacted to give the title compound (815mg, 43%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 4.08-4.17 (1H, m, 5-H), 4.42 (1H, d, J 6.0Hz, 2"-H), 4.75 (1H, d, J 13.7Hz, 2"-H), 6.63 (1H, dd, J 6.0, 13.7Hz, 1"-H), 6.98 (2H, d, J 8.6Hz, 3',5'-H_2), 7.32 (2H, dd, J 8.6Hz, 2',6'-H_2); m/z (NH_3DCI) 684 (MNH_4^+, 10%), 90 (100%).

c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 40b (800mg, 1.2mmol) in benzene (50ml) was reacted with manganese dioxide (1.2g) for 3 hours to give the title compound (437mg, 55%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.2Hz, 14-H_3), 4.08-4.17 (1H, m, 5-H), 4.56 (1H, d, J 6.0Hz, 2"-H), 4.89 (1H, d, J 13.6Hz, 2"-H), 6.21 (1H, s, 2-H), 6.68 (1H, dd, J 6.0, 13.6Hz, 1"-H), 7.09 (2H, d, J 8.7Hz, 3',5'-H_2), 7.88 (2H, d, J 8.7Hz, 2',6'-H_2); m/z (FAB; 3-NOBA/Na) 687 (MNa^+, 18%), 117 (100%).

d) 3R,4R-Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 40c (370mg, 0.56mmol) was deprotected to give the title compound (218mg, 87%); ν_{max} (KBr) 3436, 1600, 1502, 1440cm^{-1}; λ_{max} (EtOH) 323nm (εm 22620); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-

H_3), 4.59 (1H, dd, J 1.8, 6.1Hz, 2"-H), 4.91 (1H, dd, J 1.8, 13.6Hz, 2"-H), 6.22 (1H, s, 2-H), 6.69 (1H, dd, J 6.0, 13.6Hz, 1"-H), 7.05 (2H, d, J 8.8Hz, 3',5'-H_2), 7.88 (2H, d, J 8.8Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.5 (C-4), 42.6 (C-12), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 69.1 (C-7), 70.3 (C-6), 71.3 (C-13), 73.9 (C-5), 96.7 (C-2), 97.4 (C-2"), 116.5 (C-3',5'), 129.0 (C-1'), 129.3 (C-2',6'), 146.7 (C-1"), 160.2 (C-4'), 182.3 (C-1), 194.7 (C-3). [Found: M^+ 448.2119. $C_{24}H_{32}O_8$ requires M 448.2097]. The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 41

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-methoxymethyloxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 4-methoxymethyloxobenzaldehyde (J.P. Yardley et al, Synthesis, 1976, 244) (365mg, 2.2mmol) was reacted to give the title compound (1.25g, 91%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 3.47 (3H, s, OMe), 4.02-4.18 (1H, m, 5-H), 5.03-5.15 (1H, m, 1-H), 5.17 (2H, s, OCH_2O), 7.02 (2H, d, J 8.7 Hz, 3',5'-H_2), 7.22-7.32 (2H, m, 2',6'-H_2); m/z (NH_3, DCI), 702 (MNH_4^+, 8%), 239 (100%).

b) 3R,4R-Bistrimethylsilyloxy-2S[2,4-dioxo-4-(4-methoxymethyl-oxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 41a (1.2g, 1.75mmol) in benzene (50ml) was reacted with manganese dioxide (1.8g) for $3^1/_2$ hours to give the title compound (750mg, 62%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.49 (3H, s, OMe), 5.23 (2H, s, OCH_2O), 6.21 (1H, s, 2-H), 7.07 (2H, d, J 8.9Hz, 3',5'-H_2), 7.86

(2H, d, J 8.9Hz, 2',6'-H_2); m/z (NH_3, DCI) 683 (MNH_4^+, 15%), 90 (100%).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 41b (750mg) was deprotected to give the title compound (400mg, 78%); ν_{max} (KBr) 3421, 1602, 1507, 1454cm^{-1}; λ_{max} (EtOH) 321.5nm (εm 20,160); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 3.49 (3H, s, OMe), 5.24 (2H, s, OCH_2O), 6.21 (1H, s, 2-H), 7.08 (2H, d, J 8.9Hz, 3',5'-H_2), 7.86 (2H, d, J 8.9Hz, 2',6'-H_2); δc ($CDCl_3$) 12.8 (C-17), 20.8 (C-14), 31.7 (C-9), 39.7 (C-8), 42.7 (C-4), 42.9 (C-12), 55.8 (C-10), 56.3 (OMe), 65.7 (C-11), 69.2 (C-7), 70.3 (C-6), 71.4 (C-13), 73.7 (C-5), 94.2 (OCH_2O), 96.7 (C-2), 116.1 (C-3',5'), 127.9 (C-1'), 129.2 (C-2',6'), 160.9 (C-4'), 182.7 (C-1), 194.4 (C-3); (Found: M^+ 466.2198. $C_{24}H_{34}O_9$ requires M 466.2203). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 42

3R,4R-Dihydroxy-2S-[4-(but-1-yl)-2,4-dioxobut-1-yll-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-yl]methylprop-2-ene-1-yl but-1-yl ketone

A 1.75:1 mixture of the product from 1a (900mg, 1.5mmol) in THF (20ml) under argon at -70° was treated dropwise with a solution of n-butyllithium in hexane (1.5M, 2ml, 3mmol). After 30 minutes the mixture was worked-up and purified as in 1b to give material containing the title compound (320mg); δ_H ($CDCl_3$) inter alia 3.16 (2H, s, 2-H_2), 4.90 (1H, s, 15-H), 5.03 (1H, s, 15-H).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(but-1-yl)-2,4-dioxobut-1-yll-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl]tetrahydropyran

The material from 41a (300mg) in dichloromethane (20ml) was ozonolysed and then purified as described in 1c to give the title compound (93mg, 50%); δ_H ($CDCl_3$) inter alia 1.20 (3H, d, J 6.3Hz, 14-H_3), 5.59 (1H, s, 2-H).

c) 3R,4R-Dihydroxy-2S[4-(but-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-hydropyran

Using the method described in 5c, the product from 41b (85mg, 0.14mmol) was deprotected to give the title compound (43mg, 78%); ν_{max} (KBr) 3460, 1622, 1459cm^{-1}; λ_{max} (EtOH) 276nm (εm 9,295); δ_H ($CDCl_3$) inter alia 1.20 (3H, d, J 6.3Hz, 14-H_3), 5.60 (1H, s, 2-H); m/z (NH_3, DCI) 387 (MH^+, 100%). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 43

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-hydroxyethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-(2-Triethylsilyloxyethoxy)benzaldehyde

A solution of 4-(2-hydroxyethoxy)benzaldehyde (J. Bernstein et al, JACS, 1951, 73, 906) (996mg, 6mmol) in dichloromethane (20ml) under argon at 5° was treated with triethylamine (1.17ml, 8.4mmol) followed by triethylsilyl chloride (1.21ml, 7.2mmol). After 30 minutes the mixture warmed to room temperature and after a further 30 minutes ether was added and the mixture was washed with 5% citric acid, saturated sodium bicarbonate and brine then dried and evaporated to give the crude title compound (1.53g, 91%); δ_H ($CDCl_3$) 0.64 (6H, q, J 7.8Hz), 0.98 (9H, t, J 7.8Hz), 4.00 (2H, t, J 5.1Hz), 4.14 (2H, t, J 5.1Hz), 7.02 (2H, d, J 8.7Hz), 7.83 (2H, d, J 8.7Hz), 9.90 (1H, s).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-[2-triethylsilyloxyethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and the product from 43a (560mg, 2mmol) were reacted to give the

title compound (1.33g, 83%); δ_H ($CDCl_3$) 0.64 (6H, q, J 8.0Hz, $SiCH_2$), 0.90 (3H, d, J 7.0Hz, 17-H_3), 0.98 (9H, t, J 8.0Hz, $SiCH_2Me$), 1.18 (3H, d, J 6.3Hz, 14-H_3), 5.07-5.18 (1H, m, 1-H), 6.89 (2H, d, J 8.6Hz, 3',5'-H_2), 7.28 (2H, d, J 8.6Hz, 2',6'-H_2); m/z (NH_3.DCI) 816 (MNH_4^+, 5%), 90 (100%).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-[2-triethylsilyloxyethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 43b (1.3g, 1.63mmol) in benzene (70ml) was reacted with manganese dioxide (2.7g) for $3^1/_2$ hours to give the title compound (713mg, 55%); δ_H ($CDCl_3$) inter alia 0.65 (6H, q, J 7.9Hz, $Si(CH_2Me)_3$), 0.90 (3H, d, J 7.0Hz, 17-H_3), 0.98 (9H, t, J 8.0Hz, $Si(CH_2Me)_3$), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.12 (2H, t, J 4.9Hz, 1"-H_2), 6.20 (1H, s, 2-H), 6.95 (2H, d, J 8.7Hz, 3',5'-H_2), 7.87 (2H, d, J 8.7Hz, 2',6'-H_2); m/z (FAB: thioglycerol) 797 (MH^+, 10%), 157 (100%).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-hydroxyethoxy]phenyl)buty-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 43c (700mg, 0.88mmol) was deprotected to give the title compound (294mg, 72%); ν_{max} (KBr) 3421, 1603, 1508, 1451cm^{-1}; λ_{max} (EtOH) 324.5nm (εm 20,790); δ_H ($CDCl_3/d_4$-MeOH) inter alia 0.93 (3H, d, J 7.1Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 4.14 (2H, t, J 4.8Hz, 1"-H_2), 6.23 (approx. 1H, s, 2-H), 6.98 (2H, d, J 8.9Hz, 3',5'-H_2), 7.86 (2H, d, J 8.9Hz, 2',6'-H_2); δc ($CDCl_3/d_4$-MeOH) 12.3 (C-17), 20.3 (C-14), 31.5 (C-9), 39.6 (C-8), 41.7 (C-4), 42.5 (C-12), 55.6 (C-10), 60.9 (C-11), 65.4 (C-2"), 68.6 (C-7), 69.5 (C-1"), 70.1 (C-6), 70.7 (C-13), 73.9 (C-5), 96.4 (C-2), 114.4 (C-3',5'), 127.1 (C-1'), 129.1 (C-2',6'), 162.3 (C-4'), 182.7 (C-1), 193.5 (C-3); m/z (FAB: Glycerol) 467 (MH^+, 30%), 185 (100%). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 44

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3-fluorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S-3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 3-fluorobenzaldehyde (0.23ml, 2.2mmol) were reacted to give the title compound (0.998g, 78%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 5.08-5.24 (1H, m, 1-H), 6.91-7.37 (4H, m, 2',4',5',6'-H_4); (Found M^+ 642.3237. $C_{31}H_{55}O_3FSi_3$ requires 642.3240).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 44a (0.99g, 1.5mmol) in benzene (70ml) was reacted with manganese dioxide (2.0g) for $3^1/_2$ hours to give the title compound (489mg, 49%); δ_H ($CDCl_3$) inter alia 0.91 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.4Hz, 14-H_3), 6.24 (1H, s, 2-H), 7.16-7.26 (1H, m, 3'-H), 7.37-7.48 (1H, m, 4'-H), 7.58-7.71 (2H, m, 2',6'-H_2); m/z (NH_3.DCI) 641 (MH^+, 30%), 90 (100%).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 44b (480mg) was deprotected to give the title compound (229mg, 76%); ν_{max} (KBr) 3423, 1581, 1455, 1380cm^{-1}; λ_{max} (EtOH) 312nm (εm 15,735); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 6.9Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 6.24 (1H, s, 2-H), 7.17-7.69 (4H, m, 2',4',5',6'-H_4); δc ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.6 (C-8), 42.7 (C-4), 42.8 (C-12), 55.6 (C-10), 61.2 (C-11), 65.6 (C-16), 68.9 (C-6), 70.2 (C-7), 71.3 (C-13), 73.8 (C-5), 97.7 (C-2), 113.8 (d, J 43.3Hz, C-4'), 119.3 (d, J 21.2Hz, C-2'), 122.7 (C-6'), 130.2 (d, 7.9Hz, C-5'), 136.6 (d, J 7.1Hz, C-1'), 162.8 (d, J247.3Hz, C-3'), 180.6 (C-1), 191.3 (C-3). (Found: M^+ 424.1898. $C_{22}H_{29}O_7F$ requires M 424.1897). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 45

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-fluorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 2-fluorobenzaldehyde (0.23ml, 2.2mmol) were reacted to give the title compound (850mg, 66%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.06-4.19 (1H, m, 5-H), 5.40-5.50 (1H, m, 1-H), 6.87-7.06 (1H, m, 5'-H), 7.14-7.32 (2H, m, 4',6'-H_2), 7.52-7.60 (1H, m, 3'-H); m/z (NH_3.DCI) 660 (MMH_4^+, 15%), 90 (100%).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 45a (730mg) in benzene (50ml) was reacted with manganese dioxide (1.65g) for $3^1/_2$ hours to give the title compound (480mg, 67%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 6.38 (1H, d, J 1.2Hz, 2-H), 7.07-7.18 (1H, m, Ar-H), 7.20-7.26 (1H, m, Ar-H), 7.42-7.53 (1H, m, Ar-H), and 7.90-7.99 (1H, m, Ar-H); m/z 640 (M^+, 0.5%), 625(1), 165(53), 117(92), and 73(100). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 45b (0.110g, 0.17mmol) was deprotected to give the title compound (0.053g, 67%); ν_{max} (KBr) 1610, 1587, 1459, 1112, 1043, and 771cm^{-1}; λ_{max} (EtOH) 312nm (εm 15,920); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 6.39 (1H, s, 2-H), 7.08-7.30 (2H, m, 2Ar-H), 7.42-7.55 (1H, m, Ar-H), and 7.87-7.99 (1H, m, Ar-H); m/z (NH_3DCI) 442 (MNH_4^+, 10%), 425 (MH^+, 18), and 156 (100); m/z (FAB, 3-NOBA/Na) 447 (MNa^+).

The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 46

3R,4R-Dihydroxy-2S-[4-(3,4-difluorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3,4-difluorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 3,4-difluorobenzaldehyde (0.24ml, 2.2mmol) were reacted to give the title compound (0.880g, 66%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 5.07-5.17 (1H, m, 1-H), and 7.01-7.30 (3H, m, Ar-H); m/z 660 (M^+, 0.5%), 129 (46), 117 (85), and 73 (100).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3,4-difluorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 46a (1.39g) in benzene (100ml) was reacted with manganese dioxide (2.5g) for $3^1/_2$ hours to give the title compound (780mg, 57%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 6.20 (1H, s, 2-H), 7.17-7.29 (1H, m, Ar-H), and 7.61-7.78 (2H, m, Ar-H); m/z 658 (M^+, 0.5%), 643(1), 117(73), and 73(100); m/z (FAB 3-NOBA/Na) 703 ($M-H+2Na^+$) and 681 (MNa^+). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[4-(3,4-difluorophenyl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 46b (385mg, 0.58mmol) was deprotected to give the title compound (226mg, 87%); ν_{max} (KBr) 1612, 1594, 1515, 1280, 1118, 1090, and 1043cm^{-1}; λ_{max} (EtOH)

311.5nm (εm 14,940); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, J 6.3Hz, 14-H_3), 6.19 (1H, s, 2-H), 7.19-7.31 (1H, m, Ar-H), and 7.61-7.78 (2H, m, Ar-H); δc ($CDCl_3$) 12.2 (C-17) 20.2 (C-14), 31.6 (C-9), 39.8 (C-8), 41.9 (C-4), 42.5 (C-12), 55.7 (C-10), 60.9 (C-11), 65.6 (C-16), 68.5 (C-6), 70.0 (C-7), 70.5 (C-13), 74.0 (C-5), 97.2 (C-2), 116.3 (J 19Hz) and 117.5 (J 18Hz) (C-2' and 5'), 123.8 (C-6'), 131.8 (C-1'), 149.8 and 153.0 (two overlapping dd, J 253 and 13Hz, C-3' and 4'), 180.4 (C-1), and 194.5 (C-3); m/z (FAB 3-NOBA/Na) 487 (M-H+2Na^+) and 465 (MNa^+); m/z (FAB Thioglycerol) 460 (MNH_4^+) and 443 (MH^+). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 47

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-N-(2-hydroxyethyl)-N-methylaminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 5-Bromo-2-N-(2-hydroxyethyl)-N-methylaminopyridine

2,5-Dibromopyridine (4.74g, 20mmol) in 2-(methylamino)ethanol (5ml, 62mmol) was heated at 95-110°C for 6h, and stirred at RT for 16h. The viscous oil was then diluted with water (30ml) and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with brine, dried and evaporated to give a pale yellow viscous oil (4.565g, 99%); δ_H ($CDCl_3$) 3.05 (3H, s, NCH_3), 3.70 (2H, t, J 4.7Hz, CH_2), 3.84 (2H, t, J 4.7Hz, CH_2), 4.27 (1H, br, OH, xch + D_2O), 6.45 (1H, d, J 9.0Hz, 3-H), 7.52 (1H, dd, J 9.0 and 2.5Hz, 4-H), and 8.08 (1H, d, J 2.4Hz, 6-H); m/z 232/230 (M$^+$, 18%) and 201/199 (100). (Found: M$^+$, 230.0056. $C_8H_{11}BrN_2O$ requires M, 230.0055).

b) 5-Bromo-2-N-methyl-N-(2-triethylsilyloxyethyl)amino pyridine

5-Bromo-2-N-(2-hydroxyethyl)-N-methylaminopyridine (4.53g, 19.6mmol) was dissolved in dry dichloromethane (70ml), cooled in an ice bath, and treated with triethylamine (3.8ml, 27mmol) and chlorotriethylsilane (3.95ml, 23.5mmol). After five minutes the mixture was diluted with ether, filtered and evaporated. The residue was purified by column chromatography on silica (47g), eluting with 3-5% ethyl acetate in hexane,

to give the pure product as a colourless oil (6.510g, 96%); δ_H ($CDCl_3$) 0.5-0.62 (6H, m, 3x$SiCH_2$), 0.88-0.96 (9H, m, 3xCH_3), 3.08 (3H, s, NCH_3), 3.64 (2H, d, J 5.8Hz, CH_2), 3.78 (2H, d, J 5.7Hz, CH_2), 6.42 (1H, d, J 9.1Hz, 3-H), 7.47 (1H, dd, J 9.1 and 2.5Hz, 4-H), and 8.13 (1H, d, J 2.5Hz, 6-H); m/z 347/345 (MH^+, 40%), 346/344 (M^+, 50), and 201/199(100). (Found: M^+, 344.0919. $C_{14}H_{25}BrN_2OSi$ requires M, 344.0920).

c) 2-N-Methyl-N-(2-triethylsilyloxyethyl)aminopyridine-5-carboxaldehyde

5-Bromo-2-N-methyl-N-(2-triethylsilyloxyethyl)aminopyridine (1.727g, 5mmol) was dissolved in dry THF (30ml), cooled to -90°C, and treated dropwise with n-butyllithium (1.5M, 3.67ml, 5.5mmol). The mixture was stirred at -95°C for five minutes, then N,N-dimethylformamide (1.16ml, 15mmol) added. Stirring was continued for 3/4h at -90°C, then the reaction was quenched with saturated ammonium chloride. Water was added, and the mixture extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried and evaporated. The crude product was purified by column chromatography, eluting with 10-15% ethyl acetate in hexane, to give the title compound as a pale yellow oil (1.354g, 92%); δ_H ($CDCl_3$) 0.56 (6H, q, J 7.9Hz, 3x$SiCH_2$), 0.92 (9H, t, J 7.9Hz, 3-H), 3.21 (3H, s, NCH_3), 3.72-3.88 (4H, m, 2 x CH_2), 6.58 (1H, d, J 9.0Hz, 3-H), 7.90 (1H, dd, J 9.0 and 2.2Hz, 4-H), 8.53 (1H, d, J 2.2Hz, 6-H), and 9.76 (1H, s, CHO); m/z 295 (MH^+, 60%), 294 (M^+, 55), 163 (70), and 136 (100). (Found: M^+, 294.1767. $C_{15}H_{26}N_2O_2Si$ requires M, 294.1764).

d) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-N-methyl-N-(2-triethylsilyloxyethyl)aminopyrid-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-N-methyl-N-(2-triethylsilyloxyethyl)aminopyridine-5-carboxaldehyde (0.647g, 2.2mmol) were reacted to give the title compound (1.353g, 83%); δ_H ($CDCl_3$) inter alia 0.52-0.64 (6H, m, 3x$SiCH_2$), 0.88-0.98 (12H, m, 4xCH_3), 3.11 (3H, s, NCH_3), 5.01-5.12 (1H, m, 1-H), 6.53 (1H, br d, 3'-H), 7.50 (1H, br d, 4'-H), and 8.09 (1H, d, J 2.2Hz, 6'-H); m/z (FAB, 3NOBA/Na) 835 (MNa^+) and 813 (MH^+).

e) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-N-methyl(2-triethylsilyloxyethyl)aminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 47d (1.331g, 1.64mmol) in benzene (70ml) was reacted with manganese dioxide (4.1g) for 5h to give the title compound (0.631g, 48%); δ_H ($CDCl_3$) inter alia 0.5-0.63 (6H, m, 3x$SiCH_2$), 0.87-0.97 (12H, m, 4xCH_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.19 (3H, s, NCH_3), 6.13 (1H, s, 2-H), 6.55 (1H, br d, 3'-H), 7.95 (1H, dd, J 9.1 and 2.1Hz, 4'-H), and 8.70 (1H, d, J 2.2Hz, 6'-H); m/z 810 (M^+, 1%) 293(40), 135(45), 117(78), and 73(100). (Found: M^+, 810.4524. $C_{39}H_{74}N_2O_8Si_4$ requires M, 810.4522). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-N-(2-hydroxyethyl)-N-methylaminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 47e (0.610g, 0.75mmol) was completely deprotected to give the title compound (0.325g, 90%); ν_{max} (KBr) 3423, 1603, 1521, 1403, 1279, 1111, and 1054cm^{-1}; λ_{max} (EtOH) 356nm (εm 32,162); δ_H ($CDCl_3/CD_3OD$) inter alia 0.92 (3H, d, J 7.1Hz, 17-H_3), 1.21 (3H, d, J 6.3Hz, 14-H_3), 3.16 (3H, s, NCH_3), 6.14 (1H, s, 2-H), 6.58 (1H, d, J 9.1Hz, 3'-H), 7.96 (1H, dd, J 9.1 and 2.4Hz, 4'-H), and 8.63 (1H, d, J 2.4Hz, 6'-H); δ_C ($CDCl_3/CD_3OD$) 12.5 (C-17), 20.5 (C-14), 31.8 (C-9), 37.9 (NCH_3), 39.8 (C-8), 41.5 (C-4), 42.7 (C-12), 53.4 (NCH_3), 55.8 (C-10), 61.1 (C-11), 61.2 (OCH_2), 65.7 (C-16), 68.7 (C-6), 70.2 (C-7), 70.8 (C-13), 74.2 (C-5), 95.8 (C-2), 105.9 (C-4'), 119.0 (C-5'), 148.7 (C-6'), 160.8 (C-2'), 183.1 (C-1), and 191.4 (C-3); m/z 480 (M^+, 2%) and 163 (100). (Found: M^+, 480.2471. $C_{24}H_{36}N_2O_8$ requires M, 480.2472). The n.m.r. spectra indicated that the title compound was mainly in the enolic form.

EXAMPLE 48

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(4-hydroxypiperidin-1-yl)pyrid-5-yl)but-1-yl]-5S-[2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 5-Bromo-2-(4-hydroxypiperidin-1-yl)pyridine

2,5-Dibromopyridine (3.554g, 15mmol) and 4-hydroxypiperidine (4.552g, 45mmol) were heated at 100-110°C for 1h. The mixture was diluted with water and extracted with ethyl acetate (3x40ml). The combined organic extracts were dried and evaporated to give a white solid, which was recrystallised from chloroform/ hexane to give the title compound as white crystals (3.058g, 79%); m.p. 98.5-99.5°C; found C, 46.66; H, 5.10; N, 10.89%. $C_{10}H_{13}BrN_2O$ requires C, 46.71; H, 5.10; N, 10.89%; δ_H ($CDCl_3$) 1.48-1.66 (3H, m, 3'-H, 5'-H, OH), 1.90-2.05 (2H, m, 3'-H, 5'-H), 3.10-3.25 (2H, m, 2'-H, 6'-H), 3.87-4.06 (3H, m, 2'-H, 4'-H, 6'-H), 6.58 (1H, d, J 9.1Hz, 3-H), 7.52 (1H, dd, J 9.1 and 2.5Hz, 4-H), and 8.17 (1H, d, J 2.4Hz, 6'-H; m/z 258/256, 213/211 (90), 201/199 (80), 187/185 (85), and 157/159 (69). (Found: (M^+, 256.0216. $C_{10}H_{13}BrN_2O$ requires M, 256.0211).

b) 5-Bromo-2-(4-trimethylsilyloxypiperidin-1-yl)pyridine

5-Bromo-2-(4-hydroxypiperidin-1-yl)pyridine (2.985g, 11.6mmol) was dissolved in dry dichloromethane (40ml), coled in an ice bath, and treated with triethylamine (2.1ml, 15mmol) and chlorotrimethylsilane (1.76ml, 14mmol). After $^1/_2$h the mixture was diluted with ether, filtered and evaporated. The residue was redissolved in ether, filtered and evaporated to give an off-white crystalline solid (3.797g, 99%); δ_H ($CDCl_3$) 0.14 (9H, s, $Si(CH_3)_3$), 1.49-1.66 (2H, m, 3'-H, 5'-H), 1.75-1.90 (2H, m, 3'-H, 5'-H), 3.11-3.25 (2H, m, 2'-H, 6'-H), 3.82-3.99 (3H, m, 2'-H, 4'-H, 6'-H), 6.57 (1H, d, J 9.1Hz, 3-H), 7.50 (1H, dd, J 9.1 and 2.5Hz, 4-H), and 8.17 (1H, d, J 2.4Hz, 6-H); m/z 330/328 (M^+, 80%), 211/213 (100), and 73(74). (Found: M^+, 328.0606. $C_{13}H_{21}BrN_2OSi$ requires M, 328.0607).

c) 2-(4-Trimethylsilyloxypiperidin-1-yl)pyridine-5-carboxaldehyde

Using the method described in 47c, 5-bromo-2-(4-trimethylsilyloxy-piperidin-1-yl)pyridine (1.647g, 5mmol) was reacted to give the title compound as yellow crystals (0.932g, 67%); δ_H ($CDCl_3$) 0.15 (9H, s, $Si(CH_3)_3$), 1.51-1.69 (2H, m, 3'-H, 5'-H), 1.77-1.92 (2H, m, 3'-H, 5'-H), 3.44-3.58 (2H, m, 2'-H, 6'-H), 3.92-4.13 (3H, m, 2'-H, 4'-H, 6'-H), 6.68 (1H,

d, J 9.1Hz, 3-H), 7.91 (1H, dd, J 9.1 and 2.3Hz, 4-H), 8.54 (1H, d, J 2.3Hz, 6-H), and 9.76 (1H, s, CHO); m/z 278 (M^+, 60%), 263 (38), 209 (78), 161 (100), and 107 (69). (Found: M^+, 278.1454. $C_{14}H_{22}N_2O_2Si$ requires M, 278.1451).

d) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-(4-trimethylsilyloxypiperidin-1-yl)pyrid-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-(4-trimethylsilyloxypiperidin-1-yl)pyridine-5-carboxaldehye (0.613g, 2.2mmol) were reacted to give the title compound (1.135g, 71%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.02-5.15 (1H, m, 1-H), 6.68 (1H, br d, 3'-H), 7.53 (1H, br d, 4'-H), and 8.13 (1H, d, J 2.2Hz, 6'-H); m/z (NH_3, DCI) 797 (MH^+, 15%) and 279 (100); m/z 796 (M^+, 0.2%), 278(31), 129(74), and 73(100). (Found: M^+, 796.4364. $C_{38}H_{72}N_2O_8Si_4$ requires M, 796.4366).

e) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-(4-trimethylsilyloxypiperidin-1-yl)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 48d (1.120g, 1.4mmol) in benzene (70ml) was reacted with manganese dioxide (2.9g) for 3h to give the title compound (0.633g, 57%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 6.13 (1H, s, 2-H), 6.6-6.72 (1H, m, 3'-H), 7.95 (1H, br d, 4'-H), and 8.70 (1H, d, J 2.3Hz, 6'-H); m/z (NH_3 DCI) 795 (MH^+, 15%), 251(32), 92(52), and 90(100); m/z 794 (M^+, 0.5%), 277 (100), 117 (76), and 73 (96). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(4-hydroxypiperidin-1-yl)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 48e (0.600g, 0.75mmol) was completely deprotected to give the title compound (0.240g, 63%); m.p. 137-138°C (chloroform/ethyl acetate/hexane); ν_{max} (KBr)

3453, 1608, 1500, 1440, 1357, 1250, and 1075cm^{-1}; λ_{max} (EtOH) 358nm (ε_m 38,099); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.2Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 1.34-1.58 (3H, m, 12-H, 3"-H, 5"-H), 1.86-2.02 (3H, m, 8-H, 3"-H, 5"-H), 4.15-4.28 (2H, m, 2"-H), 6"-H), 6.26 (1H, s, 2-H), 6.85 (1H, d, J 9.2Hz, 3'-H), 7.99 (1H, dd, J 9.2 and 2.4Hz, 4'-H), and 8.67 (1H, d, J 2.3Hz, 6'-H); δ_C (CD_3OD) 12.2 (C-17), 20.2 (C-14), 32.9 (C-9), 34.7 (C-3" and 5"), 41.6 (C-8), 42.0 (C-4), 43.5 (C-2" and 6"), 43.7 (C-12), 56.8 (C-10), 61.2 (C-11), 66.3 (C-16), 68.3 (C-4"), 69.8 (C-6), 70.6 (C-13), 71.5 (C-7), 75.5 (C-5), 96.6 (C-2), 107.1 (C-4'), 120.1 (C-5'), 137.4 (C-3'), 149.9 (C-6'), 161.5 (C-2'), 184.4 (C-1), and 192.4 (C-3); m/z 506 (M^+, 5%), 247(20), 220(29), and 205(100). (Found: M^+, 506.2624. $C_{26}H_{38}N_2O_8$ requires M, 506.2628). A further quantity of the title compound (0.096g, 25%) was obtained after chromatography of the mother liquors. The n.m.r. spectra indicated that the compound was essentially in the enolic form.

EXAMPLE 49

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(3-hydroxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3-Iodo-1-triethylsilyloxypropane

3-Bromopropan-1-ol (1.81ml, 20mmol) and sodium iodide (6.75g, 45mmol) in acetone (15ml) were refluxed for 1 1/2h. The mixture was cooled, filtered and reduced in volume. Water was added and the mixture extracted with ether. The combined organic extracts were washed with sodium metabisulphite solution and brine, dried and evaporated. The residue was distilled, using a water pump (15mm Hg), to give 3-iodopropan-1-ol (2.885g, 78%) b.p. 96-100°C; δ_H ($CDCl_3$) 2.04 (2H, q, J 7Hz, 2-H_2), 3.15 (1H, s, OH), 3.3 (2H, t, J 7Hz, 1-H_2), and 3.7 (2H, t, J 7Hz, 3-H_2).

3-Iodopropan-1-ol (2.79g, 15mmol) was dissolved in dry dichloromethane (30ml), cooled in an ice bath, and treated with triethylamine (2.8ml, 20mmol) and chlorotriethylsilane (3ml, 17.8mmol). After 1/2h the mixture was diluted with ether, filtered and carefully evaporated to give the title compound, which was used without further purification.

b) Ethyl 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxylate

A suspension of ethyl 2-hydroxypyridine-5-carboxylate (1.170g, 7mmol) and silver carbonate (1.930g, 7mmol) in benzene (30ml) was stirred with 3-iodo-1-triethylsilyloxypropane (15mmol) for 23h. T.l.c. showed little or no reaction, so more benzene was added and the mixture gently refluxed for 48h, then stirred at room temperature for a further 48h. The mixture was then filtered and evaporated. The crude product was separated by column chromatography, eluting with 0-20% ethyl acetate in hexane, to give: (a) recovered 3-iodo-1-triethylsilyloxypropane (1.33g, 4.4mmol); (b) the title compound (contaminated with a little of (a)) (1.55g, ca.65%); δ_H ($CDCl_3$) 0.53-0.69 (6H, m, 3x$SiCH_2$), 0.89-1.01 (9H, m, 3xCH_3), 1.39 (3H, t, J 7.1Hz, CH_3), 2.01 (2H, q, J 6.2Hz, 2'-H_2), 3.79 (2H, t, J 6.2Hz, 3'-CH_2), 4.37 (2H, q, J 7.1Hz, CO_2CH_2), 4.46 (2H, t, J 6.2Hz, 1'-H_2), 6.74 (1H, d, J 8.9Hz, 3-H), 8.15 (1H, dd, J 8.8 and 2.4Hz, 4-H), and 8.82 (1H, d, J 2.4Hz, 67-H); m/z (NH_3 DCI) 340 (MH^+, 100%); m/z 339 (M^+, 0.5%), 310(91), 252(100), and 224(45). (Found: M^+, 339.1863. $C_{17}H_{24}NO_4Si$ requires M, 339.1866); and (c) the N-alkylated compound (0.56g, 24%).

c) 2-(3-Triethylsilyloxyprop-1-oxy)pyridine-5-carboxaldehyde

Ethyl 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxylate (1.53g, 4.5mmol) was dissolved in dry THF (50ml) under argon, then diisobutylaluminium hydride (1.0M, 5ml, 5mmol) was added slowly. After stirring for $^1/_2$h, more diisobutylaluminium hydride (5ml) was added, and stirring continued for a further 1h. Methanol (11ml) and saturated sodium sulphate (14ml) were added, and the mixture stirred for 15minutes. The salts were filtered off through celite, the filtrate dried and evaporated to give the hydroxymethyl compound as a colourless oil (1.36g, 100%). This material was dissolved in dichloromethane (50ml), activated manganese dioxide (2.7g) added, and the mixture stirred for 16h. After filtering, the filtrate was evaporated to give a colourless oil. This residue was purified by column chromatography, eluting with 10% ethyl acetate in hexane, to give the title compound (0.958g, 72%); δ_H ($CDCl_3$) 0.54-0.66 (6H, m, 3x$SiCH_2$), 0.89-1.0 (9H, m, 3xCH_3), 2.02 (2H, q, J 6.2Hz, 2'-H_2), 3.80 (2H, t, J 6.2Hz, 3'-H_2), 4.51 (2H, t, J 6.3Hz, 1'-H_2), 6.82 (1H, d, J 8.8Hz, 3-H), 8.06 (1H, dd, J 8.7 and 2.4Hz, 4-H), 8.62 (1H, d, J 2.4Hz, 6-H), and 9.95 (1H, s, CHO); m/z (NH_3 DCI) 296 (MH^+, 100%); m/z 296 (MH^+, 1%), 266

(M-Et$^+$, 68), 208 (100), and 124 (70). (Found: MH$^+$, 296.1681. $C_{15}H_{26}NO_3Si$ requires M, 296.1682. Found M-Et$^+$, 266.1203. $C_{13}H_{20}NO_3Si$ requires M, 266.1212).

d) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-(3-triethylsilyloxyprop-1-oxy)pyrid-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxaldehyde (0.650g, 2.2mmol) were reacted to give the title compound (1.454g, 89%); δ_H ($CDCl_3$) inter alia 0.54-0.65 (6H, m, 3x$SiCH_2$), 0.86-1.00 (12H, m, 4xCH_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 1.94-2.05 (2H, m, 2"-H_2), 4.12 (1H, dt, J 9.6 and 2.9Hz, 5-H), 4.38 (2H, t, J 6.2Hz, 1"-H_2), 5.09-5.18 (1H, m, 1-H), 6.73 (1H, d, J 8.5Hz, 3'-H), 7.60-7.68 (1H, m, 4'-H), and 8.11 (1H, d, J 2.2Hz, 6'-H); m/z 813 (M$^+$, 0.4%), 266(56), 208(72), 117(61), and 73(100). (Found: M$^+$, 813.4509. $C_{39}H_{75}NO_9Si_4$ requires M, 813.4519).

e) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-(3-triethylsilyloxyprop-1-oxy)pyrid-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxaldehyde (0.650g, 2.2mmol) were reacted to give the title compound (1.454g, 89%); δ_H ($CDCl_3$) inter alia 0.54-0.65 (6H, m, 3x$SiCH_2$), 0.86-1.00 (12H, m, 4xCH_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 1.94-2.05 (2H, m, 2"-H_2), 4.12 (1H, dt, J 9.6 and 2.9Hz, 5-H), 4.38 (2H, t, J 6.2Hz, 1"-H_2), 5.09-5.18 (1H, m, 1-H), 6.73 (1H, d, J 8.5Hz, 3'-H), 7.60-7.68 (1H, m, 4'-H), and 8.11 (1H, d, J 2.2Hz, 6'-H); m/z 813 (M$^+$, 0.4%), 266(56), 208(72), 117(61), and 73(100). (Found: M$^+$, 813.4509. $C_{39}H_{75}NO_9Si_4$ requires M, 813.4519).

e) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-(3-triethylsilyloxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 49d (1.426g, 1.75mmol) in benzene (70ml) was reacted with manganese dioxide (3.5g)

for 3h to give the title compound (0.770g, 54%); δ_H ($CDCl_3$) inter alia 0.55-0.66 (6H, m, 3x$SiCH_2$), 0.87-1.0 (12H, m, 4xCH_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 1.95-2.06 (2H, m, 2"-H_2), 4.46 (2H, t, J 6.3Hz, 1"-H_2), 6.19 (1H, s, 2-H), 6.77 (1H, d, J 8.8Hz, 3'-H), 8.06 (1H, dd, J 8.7 and 2.5Hz, 4'-H), and 8.70 (1H, d, J 2.3Hz, 6'-H); m/z 811 (M^+, 0.1%), 782(2), 117(68), and 73(100); m/z (NH_3 DCI) 812 (MH^+, 1%), 191(25), 132(45), and 90(100). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(3-hydroxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 49e (0.740g, 0.91mmol) was completely deprotected to give the title compound (0.286g, 65%); ν_{max} (KBr) 3487, 1604, 1493, 1313, 1293, and 1058cm^{-1}; λ_{max} (EtOH) 319nm (ε_m 20,731); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.2Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 1.91-2.08 (3H, m, 8-H, 2"-H_2), 3.73 (2H, t, J 6.3Hz, 3"-H_2), 4.46 (2H, t, J 6.3Hz, 1"-H_2), 6.36 (1H, s, 2-H), 6.86 (1H, d, J 8.8Hz, 3'-H), 8.17 (1H, dd, J 8.8 and 2.5Hz, 4'-H), and 8.72 (1H, d, J 2.3Hz, 6'-H); δ_C (CD_3OD) 12.3 (C-17), 20.3 (C-14), 33.0 (C-9 and 2"), 41.7 (C-8), 42.5 (C-4), 43.7 (C-12), 56.7 (C-10), 59.5 (C-3"), 61.2 (C-11), 64.8 (C-1"), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.5 (C-5), 97.7 (C-2), 112.0 (C-3'), 125.6 (C-5'), 138.7 (C-4'), 148.5 (C-6'), 167.8 (C-2'), 183.0 (C-1), and 194.9 (C-3); m/z 481 (M^+, 0.5%), 138(60), and 122(100). (Found: M^+, 481.2313. $C_{24}H_{35}NO_9$ requires M, 481.2312). A further quantity of the title compound (0.122g, 28%) was obtained after chromatography of the mother liquors. The n.m.r. spectra indicated that the compound was essentially in the enolic form.

EXAMPLE 50

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxythiazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-Methoxythiazole-5-carboxaldehyde

2-Methoxythiazole (contained 25% 2-bromothiazole, 0.50g, 4.3mmol) was dissolved in THF (20ml), cooled to -70%, and treated dropwise with n-

butyllithium (1.5M, 3.2ml, 4.8mmol). The mixture was stirred for 75 minutes, then N,N-dimethylformamide (1.16ml, 15mmol) added. Stirred for a further $1^1/_2$h, then quenched with saturated ammonium chloride and ether. The phases were separated, the organic washed with water, dried and reduced to a small volume. The crude product was purified by flash chromatography, eluting with 50% ether in pentane, to give the title compound as an orange oil (1.08g); δ_H ($CDCl_3$) 4.18 (3H, s, OCH_3), 7.86 (1H, s, 4-H), and 9.83 (1H, s, CHO), signals were also observed for solvents and a few minor impurities.

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-methoxythiazol-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 50a (max. 3.2mmol) were reacted to give the title compound (1.032g, 78%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.05 (3H, s, OCH_3), 5.21-5.32 (1H, m, 1-H), and 6.98 (1H, s, 4'-H); m/z 661 (M^+, 1%), 226 (20), 143 (39), 129 (46), 117 (72), and 73 (100). (Found: M^+, 661.2968. $C_{29}H_{55}NO_8SSi_3$ requires M, 661.2956).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxythiazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 50b (1.000g, 1.51mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 3h to give the title compound (0.431g, 43%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 4.13 (3H, s, OCH_3), 5.96 (1H, s, 2-H), and 7.75 (1H, s, 4'-H); m/z 659 (M^+, 0.1%), 644 (0.2), 184(29), 142(40), 117(89), and 73(100); m/z (NH_3 DCI) 660 (MH^+, 22%) and 90(100).. The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxythiazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 50c (0.415g, 0.63mmol) was deprotected to give the title compound (0.243g, 87%); ν_{max} (KBr) 3424, 1616, 1488, 1401, 1277, 1109, and 1048cm^{-1}; λ_{max} (EtOH) 325nm (ε_m 15,668); δ_H (CD_3OD) 0.94 (3H, d, J 7.2Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 4.13 (3H, s, OCH_3), 6.17 (1H, s, 2-H), and 7.93 (1H, s, 4'-H); δ_C (CD_3OD) 12.3 (C-17), 20.3 (C-14), 33.0 (C-9), 40.3 (C-4), 41.8 (C-8), 43.8 (C-12), 56.9 (C-10), 59.9 (OCH_3), 61.3 (C-11), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.6 (C-7), 75.5 (C-5), 97.9 (C-2), 132.0 (C-5'), 143.3 (C-4'), 160.9 (C-2'), 183.9 (C-1), and 188.1 (C-3); m/z (NH_3 DCI) 444 (MH^+, 100%), 158(33), 91(79), and 74(38); m/z 443 (M^+, 0.5%), 157(51), and 142(100). (Found: M^+, 443.1665. $C_{20}H_{29}NO_8S$ requires M, 433.1614). The n.m.r. spectra indicated that the title compound was mainly in the enolic form.

EXAMPLE 51

3R,4R-Dihydroxy-2S-[4-(cyclohexen-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(cyclohexen-1-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and cyclohexene-1-carboxaldehyde (2.2mmol) were reacted to give the title compound (0.593g, 47%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 4.13 (1H, td, J 9.5 and 3.0Hz, 5-H), 4.37-4.48 (1H, m, 1-H), and 5.72 (1H, br s, 2'-H); m/z (NH_3 DCI) 646 (MNH^+_4, 15%), 629 (MH^+, 3), 536(50), 519 (18), 128(100), and 90(83).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(cyclohexen-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 51a (0.58g, 0.92mmol) in benzene (70ml) was reacted with manganese dioxide (1.8g) for 3 1/2h to give the title compound (0.224g, 39%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J

7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 5.76 (1H, s, 2-H), and 6.90 (1H, br s, 2'-H); m/z 626 (M^+, 2%), 611 (0.5), 334 (13), 151 (33),, 117 (72), and 73 (100). (Fouind: M^+, 626.3492. $C_{31}H_{58}O_7Si_3$ requires M, 626.3491). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[4-(cyclohexen-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 51b (0.212g, 0.34mmol) was deprotected to give the title compound (0.134g, 97%); ν_{max} (KBr) 3423, 2927, 1640, 1588, 1450, 1110, and 1080cm^{-1}; λ_{max} (EtOH) 307nm (ε_m 12,570); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.5Hz, 14-H_3), 1.56-1.78 (6H, m, 9-H_2, 4'-H_2, 5'-H_2), 2.14-2.33 (4H, m, 3'-H_2, 6'-H_2), 5.86 (1H, s, 2-H), and 6.92 (1H, br s, 2'-H); δ_C (CD_3OD) 12.3 (C-17), 20.3 (C-14), 22.7, 23.2, 24.5 and 27.0 (C-3', 4', 5' and 6'), 33.0 (C-9), 41.7 (C-8), 43.3 (C-4), 43.7 (C-12), 56.9 (C-10), 61.2 (C-11), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.4 (C-5), 97.3 (C-2), 134.8 (C-1'), 137.7 (C-2'), 182.9 (C-1), 199.2 (C-3); m/z 410 (M^+, 2%), 151 (52), and 109 (100). (Found: M^+, 410.2307. $C_{22}H_{34}O_7$ requires M, 410.2305). The n.m.r. spectra indicated that the title compound was essentially in the enolic form.

EXAMPLE 52

3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-hydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[1-(furan-2-yl)-3-hydroxy-5-oxohex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 3-(furan-2-yl)propenal (0.269g, 2.2mmol) were reacted to give the title compound (1.207g, 94%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 4.7-4.8 (1H, m, 1-H), 6.14

(1H, dd, J 15.8 and 5.4Hz, 1'-H), 6.23 (1H, d, J 3.3Hz, 3"-H), 6.36 (1H, dd, J 3.3 and 1.8Hz, 4"-H), 6.49 (1H, dd, J 15.8 and 1.0Hz, 2'-H), and 7.34 (1H, d, J 1.4Hz, 5"-H); m/z 640 (M^+, 0.4%), 622 (0.4), 129 (54), 117 (100), and 73 (98). (Found: M^+, 640.3267. $C_{31}H_{56}O_8Si_3$ requires M, 640.3283).

b) 3R,4R-Bistrimethylsilyloxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 52a (1.187g, 1.85mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 2h to give the title compound (0.820g, 69%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 5.71 (1H, s, 2-H), 6.38 (1H, d, J 15.6Hz, 1'-H), 6.47 (1H, dd, J 3.4 and 1.9Hz, 4"-H), 6.57 (1H, d, J 3.4Hz, 3"-H), 7.34 (1H, d, J 15.6Hz, 2'-H), and 7.48 (1H, d, J 1.5Hz, 5"-H); m/z 638 (M^+, 1%), 623(1), 121(67), 117(89), and 73(100). (Found: M^+, 638.3140. $C_{31}H_{54}O_8Si_3$ requires M, 638.3127). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 52b (0.781g, 1.22mmol) was deprotected to give the title compound (0.477g, 93%); m.p. 150-151°C; ν_{max} (KBr) 1632, 1594, 1458, 1115, 1017, and 756cm^{-1}; λ_{max} (EtOH) 358nm (ε_m 33,626); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 5.82 (1H, s, 2-H), 6.43 (1H, d, J 15.7Hz, 1'-H), 6.54 (1H, dd, J 3.4 and 1.9Hz, 4"-H), 6.71 (1H, d, J 3.4Hz, 3"-H), 7.36 (1H, d, J 15.7Hz, 2'-H), and 7.62 (1H, d, J 1.4Hz, 5"-H); δ_C (CD_3OD) 12.2 (C-17), 20.3 (C-14), 33.0 (C-9), 41.7 (C-8), 43.7 (C-12), 44.1 (C-4), 56.8 (C-10), 61.3 (C-11), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.3 (C-5), 102.5 (C-2), 113.5, 115.4, 121.3, 127.2, and 146.2 (C-1', 2', 3", 4" and 5"), 153.1 (C-2") (C-3 and 1 not visible); m/z 422 (M^+, 4%), 163 (40), and 121(100). (Found: M^+, 422.1946. $C_{22}H_{30}O_8$ requires M, 422.1941). The spectra indicated that the title compound was essentially in the enolic form.

EXAMPLE 53

3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[3-hydroxy-1-(4-methoxyphenyl)-5-oxohex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristimethylsilylmonone (1.038g, 2mmol) and 4-methoxycinnamaldehyde (0.357g, 2.2mmol) were reacted to give the title compound (1.200g, 88%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 3.81 (3H, s, OCH_3), 4.68-4.78 (1H, m, 1-H), 6.07 (1H, dd, J 15.9 and 6.1Hz, 1'-H), 6.58 (1H, d, J 15.9Hz, 2'-H), 6.85 (2H, d, J 8.7Hz, 2"-H, 6"-H), and 7.31 (2H, d, J 8.7Hz, 3"-H, 5"-H); m/z (NH_3 DCI) 698 (MNH_4^+, 5%), 680 (MH^+, 1), 180(38), 163(100), and 90(52).

b) 3R,4R-Bistrimethylsilyloxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 53a (1.157g, 1.70mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 2h to give the title compound (0.840g, 73%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 3.84 (3H, s, OCH_3), 5.71 (1H, s, 2-H), 6.36 (1H, d, J 15.9Hz, 1'-H), 6.90 (2H, d, J 8.8Hz, 2"-H, 6"-H), 7.47 (2H, d, J 8.8Hz, 3"-H, 5"-H), and 7.56 (1H, d, J 15.9Hz, 2'-H); m/z 678 (M^+, 0.4%), 663 (0.7), 161(82), 117(63), and 73(100). (Found: M^+, 678.3451. $C_{34}H_{58}O_8Si_3$ requires M, 678.3440). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 51b (0.815g, 1.2mmol) was deprotected to give the title compound (0.468g, 84%); m.p. 130-132°C; ν_{max} (KBr) 3495, 1636, 1588, 1511, 1251, 1174, and 1114cm^{-1}; λ_{max} (EtOH) 359nm (ε_m 35,962); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.0Hz,

17-H_3), 1.19 (3H, d, J 6.5Hz, 14-H_3), 3.82 (3H, s, OCH_3), 5.82 (1H, s, 2-H), 6.51 (1H, d, J 15.9Hz, 1'-H), 6.95 (2H, d, J 8.8Hz, 2"-H, 6"-H), and 7.54 (3H, 2d, J 15.9 and 8.8Hz, 2'-H, 3"-H, 5"-H); δ_C ($CD_3OD/CDCl_3$) 12.2 (C-17), 20.3 (C-14), 32.6 (C-9), 41.1 (C-8), 43.3 (C-12), 43.7 (C-4), 55.8 (OCH_3), 56.6 (C-10), 61.1 (C-11), 66.2 (C-16), 69.4 (C-6), 70.5 (C-13), 71.1 (C-7), 75.0 (C-5), 101.8 (C-2), 115.1 (C-2" and 6"), 121.0 (C-2'), 128.7 (C-1"), 130.4 (C-3" and 5"), 140.6 (C-1'), 162.3 (C-4"), 178.1 (C-1), and 199.4 (C-3); m/z 462 (M^+, 0.6%) and 161(100). (Found: M^+, 462.2270. $C_{25}H_{34}O_8$ requires M, 462.2254). The n.m.r. spectra indicated that the title compound was essentially in the enolic form.

EXAMPLE 54

3R,4R-Dihydroxy-2S-(3,5-dioxo-1-phenylhex-1-yn-6-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-(3-hydroxy-5-oxo-1-phenylhex-1-yn-6-yl)-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and phenylpropynal (0.27ml, 2.2mmol) were reacted to give the title compound (1.139g, 86%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 5.00-5.10 (1H, m, 1-H), and 7.27-7.49 (5H, m, Ar-H); m/z 648 (M^+, 6%), 117(80), and 73(100). (Found: M^+, 648.3346. $C_{33}H_{56}O_7Si_3$ rquires M, 648.334).

b) 3R,4R-Bistrimethylsilyloxy-2S-(3,5-dioxo-1-phenylhex-1-yn-6-yl)-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

The product from 52a (0.660g, 1mmol) in dichloromethane (60ml) was stirred with manganese dioxide (active black, 1.38g) at room temperature for 75 minutes. After this time the mixture was filtered and the filtrate evaporated. The crude product was purified by column chromatography, eluting with 8-10% ethyl acetate in hexane, to give the title compound (0.328g, 50%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.3Hz, 14-H_3), 5.95 (1H, s, 2-H), and 7.32-7.60 (5H, m, Ar-H); m/z 646 (M^+, 0.2%), 631 (0.6), 258(28), 186(41), 117(46), and 73(100).

(Found: M+, 646.3164. $C_{33}H_{54}O_7Si_3$ requires M, 646.3177). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-(3,5-dioxo-1-phenyl(hex-1-yn-6-yl))-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 54b (0.320g, 0.49mmol) was deprotected to give the title compound (0.117mg, 55%); ν_{max} (KBr) 3419, 2203, 1602, 1443, 1110, 1043, and 758cm^{-1}; λ_{max} (EtOH) 328nm (ε_m 20,521); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 5.98 (1H, s, 2-H, exchanging rapidly), and 7.38-7.61 (5H, m, Ar-H); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 36.4 (C-4), 39.7 (C-8), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 68.7 (C-6), 70.1 (C-7), 71.2 (C-13), 73.7 (C-5), 85.1 and 94.3 (C≡C), 105.6 (C-2), 120.3 (C-1'), 126.0-132.6 (C-Ar), C-1 and C-3 assignments uncertain as all forms rapidly interconverting; m/z 430 (M+, 18%), 412(5), 200(30), 186(100), and 110(66). (Found: M+, 430.1984. $C_{24}H_{30}O_7$ requires M, 430.1992). The spectra indicated that the title compound was mainly in the enolic form.

EXAMPLE 55

3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-Dimethylaminopyrimidine-5-carboxaldehyde

5-Bromo-2-chloropyrimidine was converted, using the methods described in 30a, to the title compound (0.495g, 52%); δ_H ($CDCl_3$) 3.31 (6H, s, $N(CH_3)_2$), 8.73 (2H, s, 4-H, 6-H), and 9.77 (1H, s, CHO); m/z 151 (M+, 100%), 136(55), 122(74), and 95(45). (Found: M+, 151.0747. $C_9H_9N_3O$ requires M, 151.0746).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-dimethylaminopyrimidine-5-carboxaldehyde (0.333g, 2.2mmol) were reacted to give the title compound (0.997g, 74%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 3.20 (6H, s, $N(CH_3)_2$), 4.95-5.05 (1H, m, 1-H), and 8.33 (2H, s, 4'-H, 6'-H); m/z 669 (M^+, 1%), 176(48), 151(42), 129(72), 117(93), and 73(100). (Found: M^+, 669.3645. $C_{31}H_{59}N_3O_7Si_3$ requires M, 669.3661).

c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylaminopyrimidine-5-yl)-2,4-dioxobut-1-yll-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 53b (0.949g, 1.42mmol) in benzene (70ml) was reacted with manganese dioxide (3g) for 3h to give the title compound (0.421g, 45%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 3.28 (6H, s, $N(CH_3)_2$), 6.07 (1H, s, 2-H), and 8.80 (2H, s, 4'-H, 6'-H); m/z 667 (M^+, 1%), 652(2), 192(50), 150(74), and 73(100). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-2,4-dioxobut-1-yll-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 53c (0.387g, 0.58mmol) was deprotected to give the title compound (0.253g, 97%); ν_{max} (KBr) 3478, 1604, 1559, 1412, 1326, 1284, 1109, and 1059cm^{-1}; λ_{max} (EtOH) 344nm (ε_m 29,858); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.4Hz, 14-H_3), 3.26 (6H, s, $N(CH_3)_2$), 6.26 (1H, s, 2-H), and 8.81 (2H, s, 4'-H, 6'-H); δ_C ($CD_3OD/CDCl_3$) 12.2 (C-17), 20.2 (C-14), 32.6 (C-9), 37.6 ($N(CH_3)_2$), 41.2 (C-8), 41.6 (C-4), 43.3 (C-12), 56.6 (C-10), 61.1 (C-11), 66.2 (C-16), 69.4 (C-6), 70.5 (C-13), 71.1 (C-7), 75.1 (C-5), 96 (C-2), 117.3 (C-5'), 158.4 (C-4' and 6'), 163.4 (C-2'), 183.1 (C-1), and 191.6 (C-3); m/z 451 (M^+, 2%), 166(30), and 150(100). (Found: M^+, 451.2343. $C_{22}H_{33}N_3O_7$ requires M, 451.2319). The n.m.r. spectra indicated that the title compound was essentially in the enolic form.

EXAMPLE 56

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-Methoxypyrimidine-5-carboxaldehyde

Using the method described in 21a, 5-bromo-2-methyoxypyrimidine (0.58g, 3.07mmol) was converted to the title compound (0.185g, 44%); δ_H ($CDCl_3$) 4.14 (3H, s, OCH_3), 9.00 (2H, s, 4-H, 6-H), and 10.03 (1H, s, CHO); m/z 138 (M^+, 100%), 123(20), and 108(80). (Found: M^+, 138.0433. $C_6H_6N_2O_2$ requires M, 138.0429).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-methoxypyrimidin-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (0.50g, 0.97mmol) and 2-methoxypyrimidine-5-carboxaldehyde (0.134g, 0.97mmol) were reacted to give the title compound (0.384g, 61%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H_3), 1.20 (3H, d, J 6.4Hz, 14-H_3), 4.02 (3H, s, OCH_3), 5.11-5.21 (1H, m, 1-H), and 8.53 (2H, s, 4'-H, 6'-H); m/z (NH_3 DCI) 657 (MH^+, 70%), 536(31), and 139(100).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxypyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 54b (0.373g, 0.57mmol) in benzene (50ml) was reacted with manganese dioxide (1.0g) for 3h to give the title compound (0.160g, 43%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.3Hz, 14-H_3), 4.09 (3H, s, OCH_3), 6.17 (1H, s, 2-H), and 8.98 (2H, s, 4'-H, 6'-H); m/z 654 (M^+, 2%), 639(1), 117(98), and 73(100). (Found: M^+, 654.3186. $C_{30}H_{54}N_2O_8Si_3$ requires M, 654.3188).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methyoxypyrimidin-5-yl)but--1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 54c (0.15g, 0.23mmol) was deprotected to give the title compound (0.045g, 45%); δ_H (CD_3OD) 0.94 (3H, d, J 7.0Hz, 17-H_3), 1.19 (3H, d, J 6.5Hz, 14-H_3), 1.30-1.48 (1H, m, 12-H), 1.64-1.74 (2H, m, 9-H_2), 1.91-2.03 (1H, m, 8-H), 2.52 (1H, dd, J 14.8 and 9.4Hz, 4-H), 2.70 (1H, dd, J 7.5 and 2.2Hz, 11-H), 2.81 (1H, dt, J 5.7 and 2.2Hz, 10-H), 2.92 (1H, dd, J 14.8 and 2.9Hz, 4-H), 3.44 (1H, dd, J 9.2 and 3.0Hz, 6-H), 3.57 (1H, d, J 11.3Hz, 16-H), 3.73-3.84 (1H, m, 13-H), 3.87-3.95 (2H, m, 7-H, 16-H), 4.03 (1H, dt, J 3.0 and 9.4Hz, 5-H), 4.09 (3H, s, OCH_3), 6.42 (1H, s, 2-H), and 9.08 (2H, s, 4'-H, 6'-H); m/z 438 (M^+, 3%), 153(71), and 137(100). (Found: M^+, 438.2007. $C_{21}H_{30}N_2O_8$ requires M, 438.2002). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 57

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-azidoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-(2-Azidoethoxy)benzaldehyde

A solution of 4-(2-hydroxyethoxy)benzaldehyde (1.328g, 8mmol) in dichloromethane (30ml) was treated with triethylamine (1.34mmol, 9.6mmol) and methane sulphonyl chloride (0.7ml, 9mmol). After 1 hour the reaction mixture was diluted with dichloromethane, washed with dilute citric acid, saturated sodium hydrogen carbonate and brine then dried and evaporated.

The residue was dissolved in dichloromethane (30ml) and treated with tetramethyl guanidinium azide (1.42g, 9mmol). After 24 hours more tetramethyl guanidinium azide (1.42g, 9mmol) was added and the mixture was heated at 40°C. After 48 hours at 40°C followed by 2 days at room temperature the reaction mixture was washed with water, dilute citric acid, saturated sodium hydrogen carbonate and brine then dried and evaporated. Chromatography on silica eluting with ethyl acetate hexane mixtures gave the title compound (1.17g, 76%); υ_{max} (CH_2Cl_2) 2105, 1675, 1600cm^{-1}; δ_H ($CDCl_3$) 3.65 (2H, t, *J* 5.0Hz), 4.24 (2H, t, *J* 5.0Hz), 7.06 (2H, d, *J* 8.8Hz), 7.88 (2H, d, *J* 8.8Hz), 9.91 (1H, s).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-[2-azidoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (2.076g, 4mmol) and the product from 57a (764mg, 4mmol) were reacted to give the title compound (2.31g, 81%); δ_H ($CDCl_3$) *inter alia* 0.88 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 3.59 (2H, t, *J* 5.0Hz, ArO$\underline{CH_2}$), 5.06-5.18 (1H, m, 1-H), 6.90 (2H, d, *J* 8.6Hz, 3',5'-H_2), 7.25-7.38 (2H, m, 2',6'-H_2).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-[2-azidoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 57b (2.25g, 3.17mmol) in benzene (140ml) was reacted with manganese dioxide (4.51g), for 3 hours to give the title compound (1.35g, 60%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 3.63 (2H, t, *J* 5.0Hz, 1"-H_2), 4.22 (2H, t, *J* 5.0Hz, 2"-H_2), 6.22 (1H, s, 2-H), 6.96 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.88 (2H, d, *J* 8.8Hz, 2',6'-H_2); (Found $\underline{M}^+$, 707.3439. $C_{33}H_{57}N_3O_8Si_3$ requires $\underline{M}$ 707.3454).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-2-oxo-4-(4-[2-azidoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 57c (120mg, 0.17mmol) was deprotected to give the title compound (70mg, 90%); υ_{max} (KBr) 3424, 2112, 1604, 1507cm^{-1}; λ_{max} (EtOH) 324.5nm (ε_m 21,280); δ_H ($CDCl_3$) *inter alia* 0.94 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 4.21 (2H, t, *J* 5.2Hz, 2"-H_2), 6.21 (1H, s, 2-H), 6.98 (2H, d, *J* 8.9Hz, 3'5'-H_2), 7.86 (2H, d, *J* 8.9Hz, 2'6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.6 (C-8), 42.8 (C-4), 42.8 (C-12), 50.0 (C-1"), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 67.2 (C-2"), 69.0 (C-7), 70.3 (C-6), 171.3 (C-13), 73.9 (C-5), 96.7 (C-2), 114.5 (C-3',5'), 127.5 (C-1'), 129.3 (C-2'6'), 161.8 (C-4'), 182.7 (C-1), 194.3 (C-3); $\underline{m/z}$ (NH_3DCI) 492 ($\underline{MH}^+$, 100%). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 58

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-N-methyl-N-2-pyridylaminoethoxy}phenyl)but-1-yl-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-{2-N-methyl-N-2-pyridylaminoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (518mg, 1mmol) and 4-(2-N-methyl-N-2 pyridylaminoethoxy)benzaldehyde (256mg, 1mmol) were reacted to give the title compound (580mg, 75%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, 7.0Hz, 17-H_3), 1.20 (3H, d, 6.3Hz, 14-H_3), 3.15 (3H, s, N-Me), 5.06-5.16 (1H, m, 1-H), 6.48-6.59 (2H, m, Ar-H), 6.88 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.21-7.30 (2H, m, Ar-H), 7.41-7.52 (1H, m, Ar-H), 8.03-8.19 (1H, m, Ar-H); m/z (NH_2 DCI) 775 (MH^+, 5%), 257 (100%).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-{2-N-methyl-N-2-pyridylaminoethoxy}phenyl)but-1-yl-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 58a (560mg, 0.72mmol) in benzene (60ml) was reacted with manganese dioxide (1.12g) for 4 hours to give the title compound (277mg, 49%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 3.16 (3H, s, N-Me), 4.26 (2H, t, *J* 5.5Hz, 1'-H_2), 6.20 (1H, s, 2-H), 6.48-6.62 (2H, m, 3''',5'''-H_2), 6.94 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.47 (1H, dd, *J* 1.9, 7.1Hz, 5'''-H), 7.84 (2H, d, *J* 8.8Hz, 3',6'-H_2), 8.18 (1H, dd, *J* 1.4, 4.8Hz, 6'''-H_2); (Found: M^+, 772.3983. $C_{39}H_{64}N_2O_8Si_3$ requires M 772.3971).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-N-methyl-N-2-pyridylaminoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 58b (250mg, 0.32mmol) was deprotected to give the title compound (180mg, 94%); υ_{max} (KBr) 3423, 1599, 1558, 1499, 1452cm^{-1}; λ_{max} (EtOH) 324.5nm (ε_m

25,150), 248.5 (18,530); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 3.13 (3H, s, N-Me), 4.27 (2H, t, *J* 5.5Hz, 1''-H_2), 6.21 (1H, s, 2-H), 6.53 (1H, d, *J* 8.7Hz, 3'''-H), 6.58 (1H, dd, *J* 5.0, 6.8Hz, 5'''-H), 6.95 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.48 (1H, dd, *J* 1.9, 7.1Hz, 4'''-H), 7.86 (2H, d, *J* 8.8Hz, 3',6'-H_2), 8.17 (1H, d, *J* 4.9Hz, with further fine coupling, 6'''-H); δ_C ($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 37.8 (N-Me), 39.6 (C-8), 42.7 (C-4), 42.8 (C-12), 49.3 (C-1''), 55.7 (C-10), 61.2 (C-11), 65.6 (C-16), 66.7 (C-2''), 69.2 (C-7), 70.3 (C-6), 71.3 (C-13), 73.8 (C-5), 96.4 (C-2), 105.7 (C-2'''), 111.9 (C-5'''), 114.5 (C-3'5'), 126.7 (C-1'), 129.2 (C-2',6'), 137.3 (C-4'''), 147.8 (C-6'''), 158.2 (C-4'), 162.6 (C-2'''), 182.8 (C-1), 193.9 (C-3); m/z (NH_3 DCI) 556 (M^+, 55%), 121 (100%). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 59

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-piperidinylethoxy]phenyl)but-1-yl-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-[2-piperidinylethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.0388g, 2mmol) and 4(2-piperidinylethoxy)benzaldehyde (466mg, 2mmol) (HD Cossey *et al*, JCS, 1963, 4322) were reacted to give the title compound (1.0g, 66%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 5.08-5.18 (1H, m, 5-H), 6.87 (2H, d, *J* 8.7Hz, 3',5'-H_2), 7.23-7.34 (2H, m, 2',6'-H_2).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-[2-piperidinylethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 59a (1.0g, 1.3mmol) in benzene (70ml) was reacted with manganese dioxide (1.5g) for 3 hours to give the title compound (454mg, 45%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, *J* 7.0Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 6.20 (1H, s, 2-H), 6.93 (2H, d,

J 8.8Hz, 3',5'-H_2), 7.87 (2H, d, *J* 8.8Hz, 2',6'-H_2); (Found: M+, 749.4181. $C_{38}H_{67}NO_8Si_3$ requires M 749.4175).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-piperidinylethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 59b (450mg, 0.6mmol) was deprotected to give the title compound (180mg, 56%); υ_{max} (KBr) 3425, 2933, 1602, 1509, 1453cm^{-1}; λ_{max} (EtOH) 326nm (ε_m 2000); δ_H ($CDCl_3$) *inter alia* 0.93 (3H, d, *J* 7.1Hz, 17-H_3), 1.22 (3H, d, *J* 6.3Hz, 14-H_3), 6.20 (1H, s, 2-H), 6.96 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.85 (2H, d, *J* 8.8Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.8 (C-17), 20.9 (C-14), 24.2 (C-4'''), 25.9 (C-3''',5'''), 31.8 (C-9), 42.7 (C-4), 43.0 (C-12), 55.2 (C-2''',6'''), 55.8 (C-10), 57.8 (C-2''), 61.3 (C-11), 65.7 (C-16), 66.3 (C-1''), 69.2 (C-7), 70.5 (C-6), 71.9 (C-13), 74.0 (C-5), 96.6 (C-2), 114.7 (C-3',5'), 127.0 (C-1'), 129.3 (C-2'6'), 162.7 (C-4'), 183.0 (C-1), 194.0 (C-3); (Found: M+, 533.3001. $C_{29}H_{43}NO_8$ requires M 533.2989). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 60

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[4-pyridylmethyloxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-(4-Pyridylmethyloxy)benzaldehyde

A solution of *p*-hydroxybenzaldehyde (436mg, 4mmol) in THF (50ml) and 0°C under argon was sequentially treated with triphenylphosphine (2.1g, 8mmol), 4-hydroxymethylpyridine (976mg, 8mmol) and diethylazodicarboxylate (1.26ml, 8mmol). After ¼ hour ice bath removed. After 1 hour reaction mixture evaporated, added ethyl acetate and 5N hydrochloric acid. Acid phase separated, covered with ethyl acetate and basified with saturated sodium hydrogen carbonate. Organic phase separated, dried and evaporated. The residue was chromatographed on silica eluting diochloromethane/ethyl acetate mixtures to give the title compound (440mg, 52%); δ_H (CD_3OD) 5.21 (2H, s, 1'-H_2), 7.04 (2H, d, *J* 8.7Hz, 3,5-H_2), 7.51 (2H, d, *J* 6.1Hz, 3',5'-H_2), 7.89 (2H, d, *J* 8.7Hz, 2,6-

H_2), 8.60 (2H, d, *J* 6.1Hz, 2',6'-H_2), 9.92 (1H, s, -CHO).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-{4-pyridylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 60a (426mg, 2mmol) were reacted to give the title compound (1.07g, 73%); δ_H ($CDCl_3$) *inter alia* 0.92 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 4.06-4.18 (1H, m, 5-H), 5.10 (2H, s, 1"-H_2), 5.10-5.18 (1H, m, 1-H), 6.93 (2H, d, *J* 8.7Hz, 3',5'-H_2), 7.23-7.39 (4H, m, Ar-H), 8.62 (2H, d, *J* 5.9Hz, 2"',6"'-H_2); m/z (NH_3 DCI) 732 (MH^+, 80%) 94 (100%).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-{4-pyridylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 60b (1.0g, 1.37mmol) in benzene (70ml) was reacted with manganese dioxide (2.25g) for 3 hours to give the title compound (600mg, 60%);a δ_H ($CDCl_3$) 0.90 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 5.16 (2H, s, 1"-H_2), 6.22 (1H, s, 2-H), 7.02 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.37 (2H, d, *J* 5.8Hz, 3"',5"'-H_2), 7.89 (2H, d, *J* 8.8Hz, 2',6'-H_2), 8.65 (2H, d, *J* 5.8Hz, 2"',6"'-H_2); (Found: M^+, 729.3545. $C_{37}H_{59}NO_8Sio_3$ requires M 729.3549.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{4-pyridylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 60c (40mg, 0.055mmol) was deprotected to give the title compound (22mg, 78%); υ_{max} (KBr) 3418, 1715, 1602, 1507, 1450cm^{-1}; λ_{max} (EtOH) 325nm (ε_m 21140); δ_H ($CDCl_3$) *inter alia* 0.92 (3H, d, *J* 7.0Hz, 17-H_3), 1.23 (3H, d, *J* 6.3Hz, 14-H_3), 5.15 (2H, s, 1"-H_2), 6.20 (2H, s, 2-H), 7.00 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.37 (2H, d, *J* 5.8Hz, 3"',5"'-H_2), 7.88 (2H, d, *J* 8.8Hz, 2',6'-H_2), 8.63 (2H, d, *J* 5.8Hz, 2",5"-H_2); m/z (NH_3 DCI) 514 (MH^+, 55%), 94 (100%). The ^1H n.m.r. spectrum indicated that the title compound was essentially

in the enolic form.

Example 61

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{5-nitrofuran-2-ylmethyloxy}phenyl) but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-(5-Nitrofuran-2-ylmethyloxy)benzaldehyde

A solution of 2-hydroxymethyl-5-nitrofuran (S. Brokerman and T. Globerman, Tet, 1974, *30*, 3873) (1.22g, 10mmol) in THF (100ml) under argon at 5°C was sequentially treated with triphenylphosphine (2.62g, 10mmol), *p*-hydroxybenzaldehyde (1.14g, 8mmol) and dimethylazodicarboxylate (1.46g, 10mmol). After 2 hours reaction mixture diluted with ethyl acetate, washed with water then dried and evaporated. The residue was chromatographed on silica eluting with hexane/dichloromethane mixtures to give the title compound (1.6g, 81%); δ_H ($CDCl_3$) 5.19 (2H, s, 1'-H_2), 6.68 (1H, d, *J* 3.7Hz, 3"-H), 7.08 (2H, d, *J* 8.7Hz, 3,5-H_2), 7.34 (1H, d, *J* 3.7Hz, 4"-H), 7.90 (2H, d, *J* 8.7Hz, 2,6-H_2).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-{5-nitrofuran-2-ylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 61a (494mg, 2mmol) were reacted to give the title compound (1.16g, 76%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 5.06 (2H, s, 1"-H_2), 5.07-5.12 (1H, m, 1-H), 6.62 (1H, d, *J* 3.8Hz, 3"'-H), 6.92 (2H, d, *J* 8.7Hz, 3',5'-H_2), 7.26-7.48 (3H, m).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-{5-nitrofuran-2-ylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 61b (1.16g, 1.52mmol) in benzene (60ml) was reacted with manganese dioxide (3.02g) for 5 hours to give the title compound (270mg, 23%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H,

d, *J* 7.0Hz, 17-H_3), 1.18 (3H, d, *J* 6.4Hz, 14-H_3), 5.13 (2H, s, 1"-H_2), 6.20 (1H, s, 2-H), 6.63 (1H, d, *J* 3.6Hz, 3"'-H), 6.96 (2H, d, *J* 9.0Hz, 3,5-H_2), 7.32 (1H, d, *J* 3.6Hz, 4"'-H), 7.90 (2H, d, *J* 8.9Hz, 2',6'-H_2); m/z (NH_3 DCI) 781 (MNH_4^+, 20%), 764 (MH^+, 50%), 112 (100%).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{5-nitrofuran-2-ylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 61c (250mg, 0.33mmol) was deprotected to give the title compound (126mg, 70%); υ_{max} (KBr) 3463, 1604, 1507, 1468cm^{-1}; λ_{max} (EtOH) 319.5nm (ε_m 30,504); δ_H (d_4-MeOH) *inter alia* 0.96 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 5.23 (2H, s, 1"-H_2), 6.36 (1H, s, 2-H), 6.85 (1H, d, *J* 3.6Hz, 3"'-H), 7.11 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.44 (1H, d, *J* 3.6Hz, 4"'-H), 7.93 (2H, d, *J* 8.8Hz, 2',6'-H_2); δ_C (CD_3OD) 12.4(C-17), 20.5 (C-14), 33.1 (C-9), 41.8 (C-8), 42.7 (C-4), 43.9 (C-12), 57.0 (C-10), 61.4 (C-11), 63.2 (C-16), 66.7 (C-2"), 70.0 (C-7), 70.9 (C-6), 71.1 (C-13), 75.7 (C-5), 97.7 (C-2), 113.4 (C-2"'), 114.3 (C-3"'), 116.0 (C-3',5'), 129.6 (C-1'), 130.4 (C-2',6'), 154.9 (C-1"'), 162.9 (C-4'), 184.1 (C-1), 195.1 (C-3); m/z (NH_3 DCI) 565 (MNH_4^+, 8%), 548 (MH^+, 20%), 112 (100%). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 62

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{furan-2-ylmethyloxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-6S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-(Furan-2-ylmethyloxy)benzaldehyde

Furfurylalcohol (0.86ml, 10mmol) was added dropwise to a cold (5°C) mixture of sodium hydride (80%, 300mg, 10mmol) in DMF (40ml). After 1 hour *p*-fluoro-benzaldehyde (1.07ml, 10mmol) was added. After 3 hours reaction mixture poured into water and extracted with ethyl acetate. Organic phase washed with dilute sodium carbonate and brine then dried and evaporated. Chromatography on silica eluting ethyl acetate/hexane mixtures gave the title compound (700mg, 35%); δ_H ($CDCl_3$) *inter alia* 5.10 (2H, s, 1'-H_2), 6.38 (1H, dd, *J* 1.9, 3.2Hz, 4"-H), 6.46 (1H, d, *J* 3.1Hz,

5"-H), 7.04 (2H, d, *J* 8.7Hz, 3,5-H_2), 7.41 (1H, bs, 3"-H), 7.86 (2H, d, *J* 8.7Hz, 2,6-H_2), 9.92 (1H, s, CHO).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-[furan-2-ylmethyloxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 62a (400mg, 2mmol) were reacted to give the title compound (686mg, 43%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 4.98 (2H, s, 1"-H_2), 5.06-5.17 (1H, m, 5-H), 6.39 (1H, dd, *J* 1.9, 3.2Hz, 4"'-H), 6.41 (1H, d, *J* 3.2Hz, 3"'-H), 6.96 (2H, d, *J* 8.6Hz, 3',5'-H_2), 7.24-7.35 (2H, m, 2',6'-H_2), 7.45 (1H, d, *J* 1.7Hz, 5"'-H); m/z (NH_3 DCI) 738 (MNH_4^+, 25%), 203 (100%).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-[furan-2-ylmethyloxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 62b (650mg, 0.9mmol) in benzene (60ml) was reacted with manganese dioxide (1.3g) for 3 hours to give the title compound (293mg, 43%); δ_H ($CDCl_3$) 0.89 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.2Hz, 14-H_3), 4.07-4.18 (1H, m, 5-H), 5.07 (2H, s, 1"-H), 6.20 (1H, s, 2-H), 6.41 (1H, dd, *J* 1.9, 3.2Hz, 4"'-H), 6.47 (1H, d, *J* 3.4Hz, 3"'-H), 7.02 (2H, d, *J* 8.9Hz, 3',5'-H_2), 7.45 (1H, d, *J* 2.0Hz, 5"'-H), 7.88 (2H, d, *J* 8.9Hz, 3',6'-H_2); m/z (NH_3 DCI) 719 (MH^+, 40%), 90 (100%).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[furan-2ylmethyloxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 62c (260mg, 0.36mmol) was deprotected to give the title compound (158mg, 87%); υ_{max} (KBr) 3424, 1715, 1603, 1507, 1452cm^{-1}; λ_{max} (EtOH) 324.5nm (ε_m 22,418); δ_H ($CDCl_3$) *inter alia* 0.92 (3H, d, 7.1Hz, 17-H_3), 1.22 (3H, d, *J* 6.3Hz, 14-H_3), 5.09 (2H, s, 1"-H), 6.20 (1H, s, 2-H), 6.40 (1H, dd, *J* 1.9, 3.1Hz, 4"'-H), 6.47 (1H, d, *J* 3.1Hz, 3"'-H), 7.04 (2H, d, *J* 8.9Hz, 3',5'-H_2), 7.88 (2H, d, *J* 8.9Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6

(C-9), 39.6 (C-8), 42.5 (C-4), 42.8 (C-12), 54.2 (C-10), 61.3 (C-11), 62.4 (C-16), 65.6 (C-1''), 69.1 (C-7), 70.3 (C-6), 71.3 (C-13), 73.9 (C-5), 96.6 (C-2), 110.4 (C-3'''), 110.6 (C-4'''), 127.3 (C-1'), 129.2 (C-2',6'), 143.6 (C-5'''), 149.5 (C-2''''), 162.0 (C-4'), 182.7 (C-1), 194.2 (C-3); m/z (NH_3 DCI) 503 (MH^+, 85%), 83 (100%). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Biological Data

The activity of the Examples 1 to 62 against various bacteria* which are important in the diseases of humans was assayed in vitro using serial dilutions in nutrient agar with 5% chocolated horse blood.

The MIC's were determined after incubation for 18h at 37°C and values in the range 0.03 to 128 mg/ml^{-1} were observed.

* H. influenzae Q1;
B. catarrhalis 1502;
S. pyogenes CN10;
S. pneumoniae PU7; and
S. aureus Oxford.

The antibacterial activity of compounds of the instant invention against Legionella organisms are assayed in the following manner:

All compounds to be tested are dissolved in distilled water.

Organism: L.pneumophila 1624, serogroup 1. The culture is thawed from frozen skim milk stocks and streaked onto supplemented buffered charcoal yeast extract agar (BCYEα, Oxoid). Three days later, colonies are suspended into tissue culture medium (TCM=Eagle's Minimal Essential Medium + Earles' salts supplemented with 10% foetal calf serum, 2mM L-glutamine and 1% non-essential amino acids) to MacFarland's barium sulphate opacity standard 0.5. The suspension is further diluted 1:100 in TCM to yield a final inoculum of 4.83 x 106

cfu/ml.

Inoculation of cells: Human foetal lung fibroblast (MRC-5) cells are grown to 80% confluency in 6-well plates. The medium is removed and the monolayers washed twice with Dulbecco's PBS and the inoculum added.

Dosing: Sixteen hours after infection (time 0h), the medium is removed and the inoculated monolayers washed twice to remove any adherent, non-intracellular, organisms. The compounds are prepared to the required concentrations (0.5, 2 and 8μg/ml) in TCM, and added to the cells. Erythromycin at 0.5 and 2μg/m is used as a control.

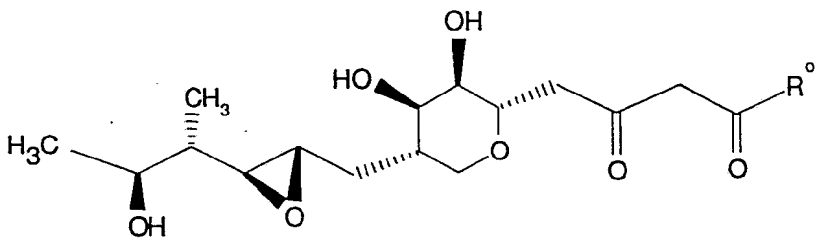
Sampling: At 0, 3, 12, 24, 36, 48 and 72h after the dose, the medium is removed from one well/treatment, and the monolayers washed twice. Sterile distilled water is added and left for 30 min to lyse the cells. After vigorous trituration, the lysate is serially diluted in Mueller Hinton brother and plated onto BYCEα and 5% horse blood agars. Colonies of L.pneumophila are counted after 72h incubation at 37°C.

Stability tests: The stability of the compounds in TCM is also examined over a 72h period. Solutions of 2 μg/ml of each of the compounds to prepared in TCM and incubated at 37°C or 4°C and aliquots are removed at intervals. The compounds of formula (I) are assayed against Bacillus subtilis ATCC 6633 and erythromycin lactobinate against Sarcina lutea NCTC 8340, using standards prepared in TCM.

Claim Set A:

What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



wherein

R^O is $(A)_n$ - $(B)_m$;

n and m are integers having a value of 0 or 1; provided that m and n may not both represent 0; and that when n is 0 then A represents a bond; and when m is 0 then B represents hydrogen;

A is an optionally substituted (C_{1-6}) alkyl, (C_{2-6}) alkenyl, or (C_{2-6}) alkynyl group; and

B is an optionally substituted (C_{3-7}) cycloalkyl, (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group.

2. A compound according to Claim 1 wherein n is 0 and m is 1, and B is a substituted or unsubstituted (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group.

3. A compound according to Claim 1 or 2 wherein B is an optionally substituted cyclohexenyl, phenyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl, or thiazolyl group.

4. A compound according to any one of Claims 1 to 3 wherein the optional substituents are independently selected up to five times by (C_{1-6})alkyl, (poly)halo(C_{1-6})alkyl, cyano, (un)substituted heterocyclyl, amino, (C_{1-6})alkanoylamino, (un)substituted mono- or di-(C_{1-6})alkylamino, hydroxy, (C_{1-6})alkoxy, -O-R_1, (C_{1-6})alkenoxy, hydroxy substituted (C_{1-6})alkoxy, (un)substituted heterocyclylthio, arylthio, arylsulphinyl, arylsulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl,

(C_{1-6})alkylsulphonyl, (un)substituted sulphamoyl, (un)substituted carbamoyl, amidino, guanidino, nitro, halogen, carboxy and salts and esters thereof, (C_{1-6}) alkylcarbonyloxy, arylcarbonyloxy, heterocyclylcarbonyloxy, or acyl groups.

5. A compound according to Claim 4 wherein R_1 is selected from (C_{2-6}) alkenyl, (C_{1-6}) alkoxy alkyl, (poly)hydroxy (C_{1-6}) alkyl, (poly)halo(C_{1-6}) alkyl, (un)substituted heteroaryl (C_{1-6}) alkyl, (un)substituted mono- or di- amino (C_{1-6}) alkyl, (un)substituted heterocyclyl (C_{1-6}) alkyl, or N-(C_{1-6} alkyl)-N- heteroaryl-(C_{1-6})alkyl.

6. A compound according to Claim 4 wherein the optional substituents are selected from methoxy, $C(O)CH_3$, methyl, cyano, chloro, fluoro, bromo, $-CH(OCH_2CH_3)_2$, nitro, -CH(O), $N(CH_3)_2$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, $-CH_2OH$, piperidine, $O-CF_3$, hydroxy, ethenyloxy, 2-hydroxyethoxy, N-(2-hydroxyethyl)-N-methylamino, 3-hydroxypropyloxy, azidoethoxy, N-methyl-N-pyridylaminoethoxy, piperidinylethoxy, pyridylmethyloxy, nitrofuranyl methyloxy, or furanylmethyloxy.

7. A compound according to Claim 1 or 3 wherein n is 1, m is 0 and B is hydrogen.

8. A compound according to Claim 1 or 3 wherein n and m are both 1.

9. A compound according to Claim 1 which is:
3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)-but-1-yl]-5S-(2S,3S,epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-hydroxyethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran; or

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran.

10. A compound according to claim 1 substantially as hereinbefore defined with reference to any one of the Examples.

11. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 9, and a pharmaceutically acceptable carrier thereof.

12. A compound acccording to any one of claims 1 to 9 for use as an active therapeutic substance.

13. A compound according to any one of claims 1 to 9 for use in treating bacterial and mycoplasmal infections.

14. Use of a compound according to any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of baceterial and mycoplasmal infections.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01760

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07H19/01; C07D405/14; C07D407/06; C07D407/14
C07D409/14; C07D413/14; C07D417/14; A61K31/70

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07H ; C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 32, no. 1, January 1989, WASHINGTON US pages 151 - 160 KLEIN L.L. ET AL 'Synthesis and activity of nonhydrolyzable pseudomonic acid analogs' cited in the application see page 153 ---	1,12
A	EP,A;0 090 603 (BEECHAM GROUP PLC) 5 October 1983 see examples ---	19
	-/--	

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16 DECEMBER 1992	13. 01. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DAY G.J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1 no. 1, January 1985, LETCHWORTH GB pages 549 - 555 CRIMMIN M.J. ET AL 'The chemistry of pseudomonic acid. Part 8. Electrophilic substitutions at C-2 and C-15 of the pseudomonic acid nucleus by means of lithium dienolates' cited in the application see page 549 - page 551	19

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201760 SA 64805

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/12/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0090603	05-10-83	JP-A- 58174379	13-10-83